Clinical Pathways in Glaucoma

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Preface

As our knowledge and understanding of glaucoma expands, there is a critical need to put this new resource for the benefit of the patient. A busy ophthalmologist or a resident-in-training always wishes for the tools that simplify the diagnosis, differential diagnosis and treatment process. It is keeping this aim in mind that the concept of *Clinical Pathways in Glaucoma* was conceived.

The twenty-two chapters were carefully selected and also include areas that are often overlooked, such as management of glaucoma in pregnancy or management of painful blind eye from glaucoma. For uniformity, each subject is discussed under the same headings: Definition, Epidemiology and Importance, Diagnosis and Differential Diagnosis, Treatment and Management, and Future Considerations. We also feel that physicians will find two additional features of this book reader-friendly. First, the discussion follows a question and answer format. These questions are designed to be clinically relevant. The reader does not have to scan through pages of textbook material to find the answer to the question at hand. Secondly, each chapter has a step-wise algorithmic approach to the management problem. There is ample cross-referencing and readers will appreciate the time and effort put forth by each author to dissect the material and present it in an understandable package.

We are very grateful to all the authors for their superb work. We would also like to thank the dedicated staff at Thieme Medical Publishers, especially Andrea L. Seils, and most recently Esther Gumpert, J. Owen Zurhellen IV, and Eric L. Gladstone. They have shown great confidence in us and have very ably kept this huge project together. Finally, we wish to dedicate this book to our families, fellows and residents without whose encouragement this work would not have been accomplished.

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Childhood Glaucoma

Kimberly S. Warren and Füsun Gökmen

Definition

How Is Childhood Glaucoma Defined?

Childhood glaucoma is a group of disorders characterized by improper development of the eye's aqueous outflow system. Another term for this group of disorders is *developmental glaucoma*. Most developmental glaucomas are seen in childhood. Infantile glaucoma is any glaucoma occurring during the first several years of life, generally accepted as the first 3 years of life. *Juvenile glaucoma* is a nonspecific term referring to any type of glaucoma occurring in later childhood or the teenage years.

What Is Buphthalmos?

Buphthalmos means "ox eye" in Latin and refers to the marked enlargement of the globe that can result from any type of glaucoma present in infancy. Hydrophthalmia refers to the high fluid content of buphthalmic eyes.

How Is Childhood Glaucoma Classified?

We can divide childhood glaucoma into three major categories (Table 1–1): (1) primary congenital glaucoma, in which the developmental anomaly is restricted to a maldevelopment of the trabecular meshwork; (2) glaucoma associated with other ocular or systemic congenital anomalies; and (3) secondary glaucoma, which includes acquired ocular diseases that can cause glaucoma.[1]

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Table 1–1. Syndrome Classification of Congenital Glaucoma (Shaffer-Weiss)

A. Primary congenital glaucoma (primary infantile glaucoma)
B. Glaucoma associated with congenital anomalies
    1. Late developing primary congenital glaucoma
    2. Familial hypoplasia of the iris with glaucoma
    3. Developmental glaucoma with anomalous superficial iris vessels
    4. Aniridia
    5. Sturge-Weber syndrome
    6. Neurofibromatosis
    7. Marfan syndrome
    8. Pierre Robin syndrome
    9. Homocystinuria
    10. Goniodysgenesis (iridocorneal mesodermal dysgenesis: Rieger's anomaly and syndrome, Axenfeld's anomaly, Peter's anomaly)
    11. Loew's syndrome
    12. Microcornea
    13. Microspherophakia
    14. Rubella
    15. Chromosomal abnormalities
    16. Broad thumb syndrome
    17. Persistent hyperplastic primary vitreous
C. Secondary glaucoma in infants
    1. Retrolental fibroplasia
    2. Tumors
        a. Retinoblastoma
        b. Juvenile xanthogranuloma
        3. Inflammation
    4. Trauma

Is There Any Other Classification of Childhood Glaucoma?

Because some developmental glaucomas do not fit in any of the specific syndromes, an anatomic classification has been proposed (Table 1–2). Anatomic defects that are apparent on examination, form the basis of this classification. Maldevelopment of the anterior segment may involve trabecular meshwork alone or the trabecular meshwork in combination with the iris and/or the cornea. Identification of the type of anatomic defect helps in determining therapy and prognosis for the infant.[2]

When Is Microcornea Seen in Childhood Glaucoma?

Microcornea may be seen in a variety of congenital anomalies, including microphthalmos, nanophthalmos, Rieger's anomaly, persistent hyperplastic primary vitreous (PHPV), congenital rubella syndrome, cornea plana, and sclera cornea. The corneal horizontal diameter is less than 10 mm. The eye is generally hyperopic but may be normal size, too. There is an increased risk of

Table 1–2. Anatomic Classification of Childhood Glaucoma

I. Isolated trabeculodysgenesis (malformation of trabecular meshwork in the absence of iris or corneal anomalies)
  A. Flat iris insertion
    1. Anterior insertion
    2. Posterior insertion
    3. Mixed insertion
  B. Concave (wraparound) iris insertion
  C. Unclassified
II. Iridotrabeculodysgenesis (trabeculodysgenesis with iris anomalies)
  A. Anterior stromal defects
    1. Hypoplasia
    2. Hyperplasia
  B. Anomalous iris vessels
    1. Persistence of tunica vasculosa lentis
    2. Anomalous superficial vessels
  C. Structural anomalies
    1. Holes
    2. Colobomata
    3. Aniridia
III. Corneotrabeculodysgenesis (usually has associated iris anomalies)
  A. Peripheral
  B. Midperipheral
  C. Central
  D. Corneal size

angle-closure glaucoma because of the shallow anterior chamber and narrow angles. Open-angle glaucoma can also be present.[3]

What Conditions May Be Associated with Macrocornea in Childhood Glaucoma?

Macrocornea is seen in patients with Axenfeld's syndrome and with X-linked recessive megalocornea. It is distinguished from the corneal stretching resulting from increased intraocular pressure (IOP) by the absence of tears in Descemet's membrane.

Where Is the Pathology in Primary Congenital Glaucoma?

The iris and ciliary body have failed to recede posteriorly, and they overlap the posterior portion of the trabecular meshwork. This appearance is similar to an eye in the seventh or eighth month of gestation rather than at full term.[4] An anterior insertion of the ciliary body muscle has also been found most specifically. The longitudinal and circular fibers of the ciliary muscle may insert into the scleral spur. The root of the iris may also insert directly into the trabecular meshwork. This malinsertion in the angle leads to blockage of aqueous humor outflow.[5]

The common defect is believed to arise from a developmental arrest during the third trimester of gestation of tissues derived from neural crest cells. The mechanism by which this developmental defect leads to aqueous outflow obstruction, in some cases, may be a paradoxical collapse of the trabecular meshwork and Schlemm's canal in response to contraction of the ciliary musculatur, although other patients may have additional developmental abnormalities in the aqueous outflow system as the possible mechanism of glaucoma.[6]

What Is Barkan's Membrane?

In 1955 Barkan[7] described a persisting fetal membrane overlying the trabecular meshwork. Recent pathologic studies have not found evidence of Barkan's membrane. This apparent membrane may be due to the observation of thickened, compact trabecular beams in the area of the meshwork.[5]

What Is the Cause of Elevated IOP in Congenital Glaucoma?

There is clinical evidence in childhood glaucoma that the obstruction to aqueous flow, with a resultant increase in IOP, is located at the level of trabecular sheets. Schlemm's canal has been found to be open both histologically and clinically and does not appear to be the site of obstruction to aqueous flow.[4,8,9]

What Are the Congenital Anomalies Associated with Childhood Glaucomas?

Table 1–1 lists the congenital anomalies associated with childhood glaucoma. Each condition is described below.

What Is the Risk of Developing Glaucoma in Familial Hypoplasia of the Iris?

This condition is characterized by hypoplasia of the anterior iris stroma, a prominent pupillary sphincter, trabeculodysgenesis, and glaucoma. Glaucoma may occur any time from birth until late adulthood, but eventually will develop in almost 100% of cases. The hereditary pattern is autosomal dominant.[10, 11]

What Are the Related Conditions with Anomalous Superficial Iris Vessels?

Irregular superficial iris vessels are generally seen with the distortion or absence of the superficial iris stroma and distortion of the pupil in newborn children with glaucoma. The cornea is usually hazy. These vessels should be differentiated from the normal radial iris vessels, which are straight and have no associated distortion of the iris tissue. Generally this is a bilateral disease.

How Often Is Aniridia Associated with Glaucoma?

Aniridia is a bilateral congenital anomaly characterized by marked hypoplasia of the iris, keratopathy, foveal hypoplasia, cataract, ectopia lentis, and optic

nerve hypoplasia.[12] Retardation of psychomotor development also may be evident. Trabeculodysgenesis of the anterior chamber angle or progressive pulling up of the residual iris stump and occlusion of the trabecular meshwork with synechiae formation are the proposed pathologies for the development of glaucoma. In most cases glaucoma does not develop until later childhood and sometimes does not develop at all.

Is Aniridia Hereditary?

Aniridia is most commonly a hereditary disorder transmitted as autosomal dominant. It also can occur sporadically, and approximately 20% of patients are found to have Wilms' tumor. There is a specific syndrome caused by a partial deletion of the short arm of chromosome 11 and includes aniridia, Wilms' tumor, mental retardation, and ambiguous genitalia.[13]

When Is Glaucoma Suspected in Sturge-Weber Syndrome?

Sturge-Weber syndrome is a flat facial hemangioma that follows the distribution of the fifth cranial nerve. A meningeal hemangioma (which can produce a seizure disorder), choroidal hemangiomas, and episcleral hemangiomas may also be present.[14] The glaucoma is present when the facial hemangioma involves the lids or conjunctiva. Facial hemangioma is usually unilateral but may be bilateral. Glaucoma occurs usually in infancy but may not develop until early adulthood in some cases. A combined mechanism of isolated trabeculodysgenesis and elevated episcleral venous pressure presumably plays a role in the pathology.[15]

When Should Glaucoma Associated with Neurofibromatosis Be Suspected?

Neurofibromatosis (von Recklinghausen's disease) is an autosomal-dominant disease characterized by multiple café-au-lait spots, neurofibromas of the skin and peripheral and central nervous system, and absence of a portion of the sphenoid bone or other skeletal defects.[16] Ocular involvement includes nodules on the iris (Lisch nodules) and eyelids, ectropion uvea, optic nerve gliomas, retinal astrocytic hamartomas, and proptosis resulting from either optic nerve gliomas or herniation of brain tissue into the orbit.

Glaucoma associated with neurofibromatosis generally is seen with neuromas involving the upper eyelid or the eye itself. Isolated trabeculodysgenesis or synechial closure caused by neurofibromatous tissue can be the mechanism of pathology. A sheet of avascular dense tissue may arise from the periphery of the iris and extend anteriorly into the angle.

What Types of Glaucoma May Be Encountered in Patients with Marfan Syndrome?

This syndrome is characterized by arachnodactyly, congenital weakness of the aorta, aortic and mitral valve disease, scoliosis, hypotonia, and ocular abnor-

malities. It is usually autosomal dominant, but 15% of cases are sporadic. Ocular involvement consists of ectopia lentis, microphakia, myopia, megalocornea, hypoplasia of the iris stroma, retinal detachment and glaucoma.[17] Two types of glaucoma are seen. Pupillary block glaucoma, secondary to malposition of the lens is one mechanism of glaucoma in these patients. The lens, usually is subluxated and held by zonules that are attenuated and often broken. Open-angle glaucoma can develop in later childhood. Iris processes can bridge the angle recess and insert well anterior to the scleral spur.[18]

What is Pierre Robin Syndrome?

This is a rare syndrome characterized by micrognathia, glossoptosis, cleft palate, and cardiac and ocular anomalies such as cataracts, high myopia, retinal detachments, microphthalmos, and childhood glaucoma.[19,20]

How Do Patients with Homocystinuria Develop Glaucoma?

Homocystinuria is an autosomal recessive disorder with a defect in the enzyme cystathionine synthetase. Patients present with light skin and hair color, osteoporosis, mental retardation, seizures, and ocular abnormalities such as retinal detachment and ectopia lentis. The lens usually is luxated inferiorly, but may move anteriorly and cause pupillary-block glaucoma.[18]

What Are the Different Presentations of Goniodysgenesis?

Axenfeld's anomaly involves corneodysgenesis of the peripheral cornea and iris, whereas Rieger's anomaly involves the midperipheral area. Central corneodysgenesis is present in Peter's anomaly.

What Is Posterior Embryotoxon?

Posterior embryotoxon is a prominent anteriorly displaced Schwalbe's line that may be present in an otherwise normal eye without glaucoma. On the other hand, extensive mesodermal strands in the angle may be accompanied by glaucoma. Axenfeld's anomaly is usually bilateral, with an autosomal-dominant pattern of inheritance. About 50% of the patients may develop glaucoma in infancy or childhood.[21]

What Is the Difference Between Rieger's Anomaly and Rieger's Syndrome?

Rieger's anomaly is a maldevelopment of iris and angle structures involving midperipheral iris adhesions to the cornea, hypoplasia of the anterior iris stroma, as well as pupillary abnormalities such as distortion of the pupil, polycoria, and correctopia. These abnormalities are usually present bilaterally, with an autosomal-dominant inheritance pattern. Other ocular abnormalities include strabismus, cataract, retinal detachment, macular degeneration, hypoplasia of the optic nerve, and chorioretinal coloboma.[22]

Rieger's syndrome is the association of the above ocular abnormalities with systemic abnormalities. Dental and facial anomalies are most common and include hypodentia, microdentia, molar hypoplasia, and hypertelorism. Other systemic anomalies include short stature, heart defects, neurologic problems, empty sella syndrome, deafness and mental deficiency. Glaucoma occurs in approximately 50% of the affected individuals.[23]

What Are the Features of Peter's Anomaly?

Peter's anomaly is manifested as central corneal opacification with adhesions of the central iris to the posterior surface of the cornea. These iris attachments arise from the collarette and attach to the cornea where there is an absence of Descemet's membrane and thinning of the posterior corneal stroma. In extreme cases the lens may adhere to the corneal endothelium and become cataractous.[24]

Another term for Peter's anomaly is *anterior chamber cleavage syndrome*. Glaucoma occurs in about 50% of the involved eyes anywhere from infancy to later childhood.

What Is Loew's Syndrome?

Loew's syndrome is a sex-linked recessive disease characterized by aminoaciduria and mental retardation in male infants. Another term for this group of conditions is *oculocerebrorenal syndrome*. Ocular abnormalities most commonly are cataracts and glaucoma. Generally, isolated trabeculodysgenesis is observed microscopically.[25]

How Is Microspherophakia Suspected?

The finding of a small spheric lens whose edges are clearly seen through a mid-dilated pupil may be suspected as microspherophakia. High myopia with shallow chamber in a young person is a characteristic of this entity. Due to the laxity of the zonules, the lens may subluxate in the posterior chamber or move anteriorly, resulting in pupillary block glaucoma.[26]

What Are the Characteristics of Glaucoma Seen in Rubella Syndrome?

The glaucoma may be present in infancy and accompanied by features of isolated trabeculodysgenesis. Glaucoma can also result from iridocyclitis. If there is any evidence of inflammation, this mechanism must be suspected. Rubella keratitis causes deep and diffuse corneal clouding, which must not be confused with corneal edema resulting from glaucoma.[27]

What Are the Chromosomal Anomalies Related to Glaucoma?

Trisomy 21, trisomy 13–15, trisomy 17–18, Turner's syndrome, and trisomy 2q may be associated with glaucoma.[28, 29]

What Is the Mechanism of Glaucoma in Persistent Hyperplastic Primary Vitreous?

This condition results from failure of atrophy of the primary vitreous and its vascular structures, and typically occurs unilaterally in a microphthalmic eye. A retrolental fibrovascular membrane attached to the posterior lens and ciliary process draws the processes into the pupillary space. Progressive opacification and swelling of the lens may cause angle-closure glaucoma, whereas contraction of the membrane may push the lens forward.

What Are the Common Childhood Secondary Glaucomas?

The common childhood secondary glaucomas are enumerated in Table 1–1. Each condition is discussed below.

When Is Glaucoma Seen in Retinopathy of Prematurity (Retrolental Fibroplasia)?

Retinopathy of prematurity is associated with a history of prematurity of the newborn. It is bilateral and nearly symmetric. One theory suggests that oxygen therapy causes vasoconstriction in the peripheral retinal vessels initially. Ischemia may invite neovascularization, which may grow through the internal limiting membrane into the vitreous in advanced cases. Eventually, the development of these retrolental fibrotic membranes may cause a forward displacement of the lens and iris and cause angle-closure glaucoma with some degree of pupillary block.[30]

What Tumors May Cause Glaucoma in Children?

Retinoblastoma is the most common intraocular tumor of childhood. The tumor may invade the iris and trabecular meshwork area. Many patients develop rubeosis iridis and intractable neovascular glaucoma.[31] *Juvenile xanthogranuloma* is an uncommon skin disease with its onset in infancy.[32] Ocular involvement is seen as a vascular, yellowish white, solitary or diffuse mass of iris. Tumor involvement of the trabecular meshwork area and ciliary body may also occur. The most common cause for glaucoma is a spontaneous hemorrhage into the anterior chamber.

What Is the Most Common Inflammatory Condition Present with Glaucoma in Children?

Chronic iridocyclitis seen in juvenile rheumatoid arthritis is rarely associated with discomfort or redness. Many patients with this "white uveitis" may present with sequelae that may include glaucoma, cataracts, and band keratopathy.[33] For other causes, see Chapter 8.

Is Traumatic Glaucoma Common in Children?

Children may present with traumatic glaucoma that is very similar to that in adults. For a complete discussion, see Chapter 13.

Epidemiology and Importance

How Common Is Childhood Glaucoma?

Childhood glaucoma, in all its forms, occurs in about 1 in 10,000 live births.[34] Primary congenital glaucoma is not a common disease. It is estimated to affect less than 0.05% of ophthalmic patients.[35] Disease is bilateral in 75% of cases. Male gender is found to have a higher incidence of the disease (65%). More than 80% of the cases are evident before the first year of life. It is the most common glaucoma of infancy, presenting as 1 in 30,000 live births.

Are There Any Genetic Considerations for Childhood Glaucoma?

The majority of cases of primary congenital glaucoma are sporadic. An autosomal recessive inheritance is reported in 10% of the cases.[19,35] The penetrance rate varies from 25 to 100%. It is also reported that the penetrance of affected siblings may be between 3 and 11%.[36] As boys were found to be affected more than girls, in this study inheritance pattern was believed to be polygenic. Genetic counseling is very helpful to the parents of affected children, as there is a 3 to 5% risk of another sibling being affected.[37]

What Are the Characteristics of the Genes Involved in Primary Congenital Glaucoma?

There are currently two genetic regions associated with the primary congenital glaucoma—GLC3A and GLC3B. The GLC3A region is on chromosome 2p21. Recently, mutations in the human cytochrome P4501B1 gene (CYP1B1) were identified in patients with GLC3A. No candidate genes have been reported for the GLC3B region, which is located on chromosome 1p36. Both genes have autosomal-recessive transmission, and glaucoma is present before 3 years of age.[38]

What Are the Genes Associated with the Secondary Glaucoma?

The PAX-6 gene located on chromosome 11p13 has been implicated in a number of ocular disorders.[38]

Diagnosis and Differential Diagnosis

How Is Childhood Glaucoma Diagnosed?

The examination and diagnosis of young children can be quite challenging. Childhood glaucoma has different presentations and can coexist with a variety of rare pediatric syndromes and congenital defects. The clinician must be aware of the different presentations of childhood glaucoma and have the knowledge to suspect the possibility of the disease in the absence of symptoms. Childhood glaucoma has been divided into three main classifications based on primary and secondary mechanisms: (1) primary, including primary infantile glaucoma and juvenile open-angle glaucoma; (2) glaucoma associated with congenital anomalies; and (3) secondary childhood glaucoma.[39] Key elements to making

an accurate diagnosis include obtaining a complete history, paying careful attention to the clinical presentation, and doing a thorough examination.

How Does Primary Infantile (Congenital) Glaucoma Present?

Primary infantile glaucoma typically presents with epiphora, photophobia, and blepharospasm. The presentation of congenital glaucoma is seen in children 3 years of age or younger. The parents will often report that the child is constantly tearing, is extremely light sensitive, and squints his or her eyes to avoid the light. These symptoms occur from corneal irritation secondary to epithelial edema caused by increased IOP.[40] Buphthalmos, or "bull's-eye"–like enlargement of the eye also can occur from the increased IOP and is recognized by an increased corneal diameter and progressive myopia. Buphthalmos occurs in children under 3 years of age because of elasticity and stretching of the ocular tissue. Additional findings include a cloudy cornea with breaks in Descemet's membrane (Haab's striae), anisometropic amblyopia, and strabismus.

How Does Juvenile Open-Angle Glaucoma Present?

In contrast to primary infantile glaucoma, juvenile open-angle glaucoma may have no external signs or symptoms. It presents after the age of 3 years and often goes undetected until advanced visual loss has occurred, with decreased central vision or extensive visual field loss. It can be detected early by screening exams if the IOP is measured and the optic nerve is evaluated.

What Is the Best Way to Examine a Child If Glaucoma Is Suspected?

Examination of the pediatric patient is often difficult and depends largely on the patient's age and ability to cooperate. Children older than 4 years of age are usually able to cooperate with slit-lamp evaluation, tonometry, and optic nerve evaluation. Gonioscopy and visual field examination are more difficult to perform on young children, but some are able to cooperate by the age of 5 to 6. By the age of 8 to 10, most children are able to perform automated visual fields and a complete ophthalmologic examination. In the younger pediatric age group (4 years and less), a mild sedative such as chloral hydrate syrup (25 to 50 mg/kg body weight) can be used in the office to perform a slit-lamp examination, applanation, gonioscopy, and fundus examination. This is not always successful, and often general anesthesia is needed to properly evaluate the child. It is important to remember that most general anesthetics lower the IOP, so this measurement should be obtained as soon as possible once the child is asleep.[41] Ketamine has been known to raise the IOP.[42]

What Are the Clinical Signs to Look for During the Examination?

It is important to know that not all childhood glaucomas have presenting symptoms, but one can make the diagnosis by clinical signs and evaluation. Increased IOP, corneal edema, increased corneal diameter, iris and corneal anomalies, gonioscopic anomalies, refractive errors, and optic disc cupping are

key elements when making a diagnosis of childhood glaucoma. Normal IOP in children is slightly lower than in adults, but 20 mm Hg can be considered the upper range of normal. A pressure of 20 mm Hg or higher should alert the physician.[43] The cornea should be examined by slit-lamp biomicroscopy for the evidence of corneal edema. Haab's striae or breaks in Descemet's membrane can be seen in congenital glaucoma as a result of increased IOP. The corneal diameter should be measured. This is best evaluated by using calipers and measuring the horizontal diameter. The normal cornea diameter in infants is 9.5 to 10.5 mm, reaching 12 mm by adulthood.[44] The iris and cornea should be inspected for anomalies. This will help in the later classification of the type of childhood glaucoma. Developmental anomalies of the iris and cornea are not seen in primary infantile glaucoma, and if present should raise the suspicion of glaucoma associated with congenital anomalies. Gonioscopy can be evaluated by the Koeppe, Goldmann, or the four-mirror hand-held lens. The iridocorneal angle differs in childhood from that in adulthood. The angle is open but the trabecular meshwork is a smooth, homogeneous membrane extending from the peripheral iris to Schwalbe's line. As the child ages the trabecular meshwork increases in pigmentation and becomes coarser.

The physician must know the difference between normal and abnormal angle features in children in order to correctly diagnosis congenital glaucoma. In congenital glaucoma the angle is open with an anterior insertion of the iris root into the trabecular meshwork. Glaucoma caused by trauma or inflammation may show angle recession or peripheral anterior synechiae, respectively. Refraction should be performed. A myopic shift may suggest glaucoma. The cup-to-disc ratio should be examined in all children evaluated for glaucoma. A ratio greater than 0.3 is unusual in normal infants but is often seen in infants with glaucoma.[45] It is useful to know that if therapy is successful, the cup-to-disc ratio may decrease in size over time. This is not always true for adults.

The diagnosis of childhood glaucoma is not based solely on one finding being abnormal. It is a clinical diagnosis based on multiple signs and symptoms. If the physician is uncertain of the diagnosis, it is best to reexamine the child in a few weeks for confirmation.

How Does One Determine If the Child Has Primary Infantile Glaucoma or Another Form of Childhood Glaucoma?

The history and examination provide the answer. Primary infantile (congenital) glaucoma is diagnosed by increased IOP and by the finding of a high insertion of the iris on the trabecular meshwork without other ocular or systemic developmental anomalies. If other ocular or developmental systemic anomalies are present, the child is classified as having glaucoma associated with congenital anomalies. If the glaucoma is acquired due to a primary problem such as trauma, inflammation, or tumors, then it is classified as secondary.

Can Other Disease Processes in Children Mimic Childhood Glaucoma?

The most common clinical features for childhood glaucoma include excessive tearing, clouding of the cornea, large corneal diameter, elevated IOP, and

increased cup-to-disc ratio. The first three are common in children less than 3 years of age, and the last two are found in all ages. There are many other pediatric disease processes that can present with similar symptoms. It is important for the ophthalmologist to be knowledgeable of these conditions so that the child can receive proper diagnosis and treatment.

What Are Other Causes of Excessive Tearing?

The most common cause of tearing in the infant is obstruction of the lacrimal drainage system. It can be unilateral or bilateral and may be accompanied by purulent discharge. Photophobia is not commonly associated with this problem. Another cause of tearing is conjunctivitis, either viral or bacterial, which is usually associated with purulent discharge and injection of the conjunctiva. Trauma with resultant corneal abrasions can cause excessive tearing in the infant and can easily be diagnosed by examination. A corneal dystrophy can cause ocular pain and tearing as seen in Meesman's corneal dystrophy secondary to epithelial vesicles. Other causes may be recurrent epithelial erosions as seen in Reis-Buckler's dystrophy.

What Are Other Causes of a Cloudy Cornea?

There are many causes of congenital cloudy cornea. Table 1–3 lists the causes of congenital clouding of the cornea. It is important for the physician to keep in mind the differential diagnosis for a cloudy cornea in the infant and not always to assume it is secondary to increased IOP.

Table 1–3. Causes of Congenital Cloudy Cornea

I. Dystrophies
   1. Congenital hereditary stromal dystrophy
   2. Congenital hereditary endothelial dystrophy
II. Dermoid
III. Sclerocornea
IV. Infection
   1. Rubella
   2. Herpes simplex virus
   3. Syphilis
V. Metabolic (inborn errors rarely present at birth)
   1. Mucopolysaccharidoses
   2. Mucolipidoses
VI. Trauma
   1. Forceps delivery with Descemet's breaks
VII. Anterior chamber cleavage syndromes—can have glaucoma associated
   1. Axenfeld-Rieger's anomaly
   2. Peter's anomaly
   3. Posterior keratoconus
VIII. Congenital glaucoma
IX. Congenital anterior staphyloma

What Dystrophies Can Cause a Cloudy Cornea in the Infant?

Both stromal and endothelial dystrophies can cause a congenital cloudy cornea. Congenital hereditary stromal dystrophy presents at birth and is autosomal dominant. It has superficial corneal clouding with a flaky or feathery appearance of the anterior stroma.[46] Congenital hereditary endothelial dystrophy may be autosomal recessive or autosomal dominant in nature. The autosomal-recessive form presents at birth with an edematous stroma, a thickened Descemet's membrane, and nystagmus. The autosomal-dominant form is usually seen between ages 1 and 2 with photophobia and progressive corneal swelling.[47]

What Is the Difference Between a Dermoid and Sclerocornea?

A corneal dermoid is a choristoma that is composed of epidermis and epidermal appendages within a fibrous stroma.[48] Most dermoids are found on the inferior temporal limbus and span approximately 8 to 10 mm. Dermoids extend into the corneal stroma and adjacent sclera. Limbal dermoids are seen in association with Goldenhar's syndrome. Dermoids can cover the visual axis or produce a large degree of astigmatism. Either of these situations can cause amblyopia and vision loss. If either case is present, excision may be warranted. Sclerocornea is a congenital condition in which the cornea is opaque, resembling the sclera, and the limbus cannot be identified.[49]

What Infections Can Cause a Cloudy Cornea in Children?

Rubella is caused by a single-stranded ribonucleic acid virus. Congenital rubella is the result of a maternal infection during the first trimester of pregnancy. The classic triad of infants born with rubella include heart defects, deafness, and cataracts. A variety of ocular abnormalities can be seen, including pigmentary retinopathy, anterior chamber anomalies, glaucoma, and microphthalmos. The central cornea is often cloudy at birth, which is caused by either an absence of or ruptures in Descemet's membrane or by congenital glaucoma.[50] Congenital syphilis is also a well-known infectious cause of childhood cloudy corneas. Congenital syphilis is caused by the spirochete *Treponema pallidum* and is passed to the fetus in utero. The classic triad of congenital syphilis consists of interstitial keratitis, Hutchinson's teeth, and deafness. The interstitial keratitis of congenital syphilis usually is a late manifestation, presenting after the age of 2 years. The interstitial keratitis is secondary to an inflammatory response to previously present spirochetes and is not due to an active infection. Both corneas are usually involved within weeks of each other. The child can present with similar symptoms of childhood glaucoma including tearing, photophobia, and blepharospasm. Perilimbal injection is also present, differing from congenital glaucoma. The inflammation is usually sectoral and involves the superior stroma. Keratic precipitates are typically present in the early stages. As the disease progresses, neovascularization develops in the deep stroma. As neovascularization becomes denser, the cornea appears pink and is referred to as a salmon patch. As the disease regresses, the cornea is often left scarred, and ghost vessels can be seen in the mid- to deep stroma.

What Metabolic Diseases of Childhood Can Cause Cloudy Corneas?

There are a number of inborn errors of metabolism that can cause congenital cloudy corneas. Fortunately, these disorders are rare, but they warrant discussing as a differential diagnosis in childhood glaucoma. These disorders are caused by an abnormal metabolism of carbohydrates and lipids. The major classifications include the mucopolysaccharidoses, the sphingolipidoses, and the mucolipidoses. Three mucopolysaccharidoses (MPSs) that cause diffuse clouding of the cornea include Hurler (MPS I-H), Scheie (MPS I-S), and Morquio (MPS IV) syndromes. Both Hurler and Scheie syndrome present with a cloudy cornea at birth and progress over the first 6 months, whereas Morquio syndrome does not show clouding of the cornea until after the age of 10. Fabry's disease, gangliosidosis type I, gangliosidosis type II (Sandhoff's disease), and Niemann-Pick disease are all disorders of sphingolipids. The most notable corneal changes seen in the sphingolipidoses consist of cornea verticillata, whorl-like lines in the corneal epithelium. This is a characteristic finding in Fabry's disease. The mucolipidoses that present at birth with a cloudy cornea include MLS II and MLS IV. Cystinosis is an amino acid metabolic disorder that has an infantile, adolescent, and adult form. The infantile form is most severe, and cystine crystals can be present in the cornea at birth. This form of the disease is associated with renal failure in early childhood.[51]

What Are the Characteristics of a Cloudy Cornea Due to Birth Trauma?

Tears in Descemet's membrane can be seen as a result of birth trauma due to forceps delivery. Classically these have been described as vertical tears, whereas Haab's striae found in congenital glaucoma have a horizontal orientation. These are only generalizations, and either horizontal or vertical tears can be found due to each of the above causes. Not all tears secondary to trauma will cause diffuse corneal edema. If edema is present from trauma, it will usually resolve over the ensuing weeks spontaneously. The edema from childhood glaucoma will resolve only after the IOP has been successfully lowered.

What Are Other Causes of a Large Cornea?

Megalocornea and high myopia are two conditions other than congenital glaucoma and childhood glaucoma associated with ocular and congenital anomalies that can cause a large cornea in children. Megalocornea is an enlarged cornea that is nonprogressive. The cornea is clear and has normal histology. The diameter of megalocornea is 13 mm or greater in horizontal diameter. Ninety percent of patients are male, and the condition is usually bilateral. A sex-linked inheritance pattern is evident. Megalocornea is usually an isolated finding but can be seen in addition with cataracts, and glaucoma secondary to angle anomalies. Large corneas can also be seen in patients with high degrees of axial myopia. These children do not display the other signs of congenital or juvenile glaucoma.

What Are Other Causes of an Abnormal Optic Nerve?

It is important to recognize congenital causes of an abnormal optic nerve and be able to differentiate these causes from the enlarged cup-to-disc ratio found in the childhood glaucomas. It is often difficult to examine the posterior pole in the pediatric population. Every effort must be made to get a good look at the nerves. At times, evaluation under anesthesia is needed if an adequate exam cannot be obtained in the office. Congenital abnormalities include an optic nerve coloboma, optic nerve pits, hypoplasia, and tilting secondary to myopia. Optic nerve pallor and atrophy can also be seen in children, and the appropriate workup must be performed to ascertain an underlying cause. Physiologic cupping must be distinguished from glaucomatous cupping. This is difficult in the pediatric population, as most children do not perform well with the traditional visual field testing. Examination of family members can often be helpful to rule out physiologic cupping, and the new nerve fiber analyzers may become quite useful in the pediatric population.

What Steps Should Be Taken When Evaluating and Diagnosing a Child for Possible Childhood Glaucoma?

This section of the chapter has dealt with the initial presentation, signs and symptoms, physical examination, and differential diagnosis of childhood glaucoma. It can be a challenging diagnosis, and a flow chart has been developed to help aid the practitioner in making the correct diagnosis (Fig. 1–1).

Treatment and Management

How Is Congenital Glaucoma Managed?

The treatment for congenital glaucoma is surgical. Medical therapy alone is not sufficient in lowering the IOP in children. A study performed at the University of Ankara, Turkey, showed that medical therapy alone in congenital glaucoma reduced the IOP to less than 21 mm Hg in 11.8% in short-term follow-up and 9.7% in the long-term.[52]

The main surgical procedures of choice remain goniotomy, trabeculotomy, or trabeculectomy, with or without antimetabolites. Goniotomy was initially described by Barkan in the 1940s. This technique requires direct visualization of the trabecular meshwork with a surgical goniolens. A goniotomy knife is then inserted 1 mm anterior to the limbus through clear cornea. The blade is passed through the anterior chamber 180 degrees from the initial entry site. The blade is then used to incise one-third of the chamber angle. The incision is aimed at the abnormal layer of tissue in front of the trabecular meshwork. If the initial goniotomy procedure fails, repeat goniotomy may be needed. The trabeculotomy creates a direct communication between the anterior chamber and Schlemm's canal. The technique was modified by Harms and Dannheim.[53]

The surgery involves creating a conjunctival flap similar to that performed in a filtering procedure. A partial-thickness limbal based scleral flap approximately 3 × 3 mm is then dissected. A radial incision is then made at the sclerolimbal junction until Schlemm's canal is entered. This can be identified by a

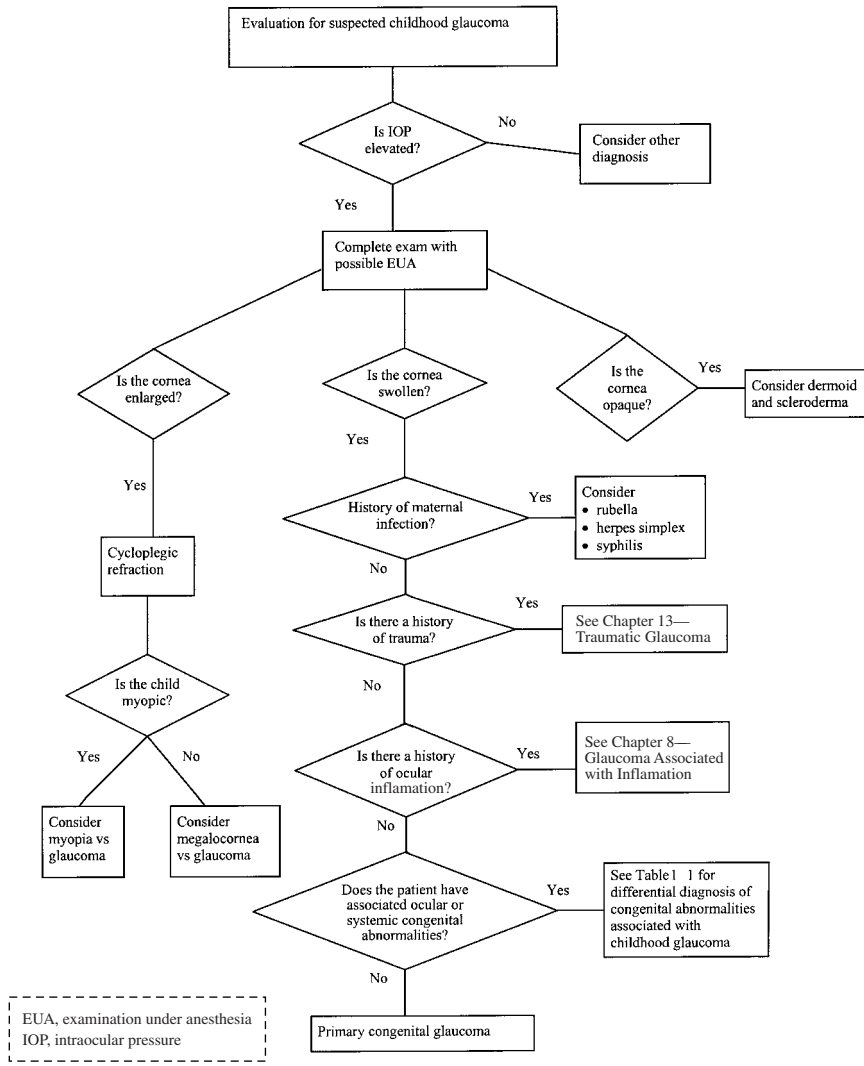

Figure 1–1. Algorithm for Evaluation of Childhood Glaucoma.

gush of aqueous humor or blood. A trabeculotome is then inserted into Schlemm's canal and rotated so the arm tears through the trabecular meshwork and enters the anterior chamber. The trabeculotome is then inserted in the other direction and the same procedure is performed. The angle is opened 180 degrees with this technique. An additional scleral flap can be made 180 degrees away from the initial site to perform the procedure, for a total of 360 degrees. The trabeculectomy procedure performed is the same in children and adults. It involves conjunctival flap either limbal or fornix based, and a partial-thickness limbal based scleral flap of approximately 3 × 3 mm. A fistulizing technique is then performed. A peripheral iridectomy is made to prevent blockage of the fis-

tula with iris incarceration. The scleral flap is then closed with 10-0 nylon sutures and the conjunctiva is reapproximated with a vascular needle. There has been recent discussion as to whether anti-metabolites should be use in the pediatric population in hopes of increasing the long-term patency of the filter. Other surgical procedures are performed in childhood glaucoma in situations where the above have failed or are not indicated. These procedures include tube-shunt surgery, with the use of valved and nonvalved implants; cyclocryoablation; cyclophotocoagulation; and ciliary-body endophotocoagulation.

What Is the Best Surgical Treatment for Childhood Glaucomas?

The three principal initial surgical procedures for childhood glaucoma are goniotomy, trabeculotomy and trabeculectomy. Goniotomy and trabeculotomy have been the traditional choice for congenital glaucoma, with both having similarly high success rates. A study done at Moorfields Eye Hospital treating congenital glaucoma with initial goniotomy showed 93% of eyes controlled at 5 years.[54] Goniotomy has both an advantage and disadvantage. The advantage is that it preserves conjunctiva if future surgery is needed, but the disadvantage is the need for a clear cornea to visualize the trabecular meshwork. The advantage to the trabeculotomy is that direct visualization of the trabecular meshwork is not needed, and if Schlemm's canal cannot be identified, the procedure can be converted into a trabeculectomy. There has been recent interest in a combined trabeculotomy and trabeculectomy as the initial procedure in uncomplicated congenital glaucoma. A recent study performed in Saudi Arabia showed a 78% operative success in eyes with no coexistent anterior segment anomalies.[55] Further studies comparing trabeculotomy, combined trabeculotomy and trabeculectomy, and trabeculectomy found that the results did not differ significantly.[56] The best surgical choice for the initial treatment of congenital glaucoma is the technique that is most comfortable for the surgeon. Goniotomy is usually reserved for children of age 3 and under. Goniotomy and trabeculotomy are the first-line procedures in congenital glaucoma at a large referral center where the surgeons are experienced with these techniques. To the general ophthalmologist who is not experienced with the former procedures, the most appropriate primary surgery is the trabeculectomy.

What Is the Role of Mitomycin C in Filtration Procedures in Children?

At times a trabeculectomy is the procedure of choice in children. The trabeculectomy can be performed as the primary procedure or after previous failed trabeculotomy/goniotomy. In either case the question of the use of an antimetabolite must be considered. It is well known that trabeculectomy can fail in the pediatric population and is contributed to a thick Tenon's layer and aggressive healing in children. A recent study evaluating the role of mitomycin C in childhood trabeculectomy showed a 1-year success rate of 76.9% in phakic patients.[57] Interestingly, the same study revealed 0% success in aphakic eyes. Success was considered to be an IOP of less than 21 mm Hg with no need for antiglaucoma medication 1 year after the surgery. A similar study performed at

Emory University School of Medicine showed a success rate of 67% ± 13% at 12 months and 59% ± 15% at 24 months. This same study identified aphakia and age of less than 1 year as significant risk factors for failure.[58] The long-term complications such as bleb leaks with hypotony and endophthalmitis must be considered when using an antimetabolite in children.

What Is the Role of Tube-Shunt Procedures in the Pediatric Population?

Tube-shunt procedures are considered in the pediatric population in children with glaucoma refractory to medical and previous surgical intervention. A study of 18 patients performed at Wills Eye Hospital revealed a 72.2% success rate at 6 months.[59] Success was considered to be an IOP between 6 and 21 mm Hg with or without glaucoma medication. At 2-year follow-up, the success rate was 44.4%, although five eyes (27.8%) had lost light perception and 12 of the 18 eyes underwent 28 additional surgical procedures to control IOP or manage tube-related complications. Tube-shunt procedures can be a surgical option for childhood glaucoma, but is usually reserved for refractory glaucoma and not as an initial therapy.

What Are the Follow-Up Considerations in Children with Childhood Glaucoma?

The child must be followed carefully to ensure that the glaucoma is stable and not progressing. Serial examinations are needed to ensure proper care. In congenital glaucoma the corneal edema is followed to ensure its resolution. A cloudy cornea can cause amblyopia and permanent vision loss. Once the corneal edema has resolved, the child is followed every 3 months to check the IOP, corneal diameter, and cup-to-disc ratio. Once the child is stable, examination can be performed every 6 months. It is important to keep in mind that amblyopia can result not only from an opaque cornea but also from anisometropia caused by a myopic shift. Careful attention must be paid to the refraction, and the child must be observed for any signs of a lazy eye. Many of these children require glaucoma medication, and the child must be watched to avoid systemic manifestation of the drugs. When using a beta-blocker, a complete history must be obtained, paying special attention to cardiac disease and a history of asthma. Pilocarpine can cause myopia and may be very difficult to tolerate, especially for children of school age.

Future Considerations

What Does the Future Hold for Early Detection of Glaucoma?

There have been recent discoveries concerning glaucoma and the field of genetics. Glaucoma loci have been grouped into three categories: primary open-angle glaucoma, primary closed-angle glaucoma, and congenital glaucoma. The congenital glaucoma group use the prefix GLC3. Primary open-angle glaucoma and primary closed-angle glaucoma use the prefix GLC1 and GLC2, respectively. There currently are two genes or genetic regions associated with

congenital glaucoma. The congenital loci are GLC3A and GLC3B. The GLC3A region is on chromosome 2p21 and the gene is CYP1B.[60] The GLC3B subtype has been located on chromosome 1p36, but no gene has been identified yet.[61] Secondary glaucomas have been linked to the PAX-6 and PITX2 genes. Aniridia and Peter's anomaly have been linked to the PAX-6 gene located on chromosome 11p13.[62,63] Axenfeld-Rieger syndrome type 1 and iridogoniodysgenesis type 2 have been linked to the PITX2 gene located on chromosome 4q25.[64,65] Although still in its infancy, mapping and cloning of glaucoma genes hold a promising future. Early detection and treatment through genetic identification could halt advanced vision loss seen in childhood glaucoma.[6]

What Are the Future Challenges of Glaucoma Genetics?

The mapping and cloning of glaucoma-related genes have been progressing. It is anticipated that the actual number of glaucoma-causing genes will be much greater than the number currently known. There is considerable phenotypic variability that will make it difficult for clinicians and geneticists to associate clinical findings with the genes involved. However, as more genes are identified, the molecular pathogenesis of glaucoma may be better understood. Early genetic screening would allow the best treatment to be used for each patient. A greater number of patients can take advantage of early detection strategies to slow the progress of this insidious disease.[6]

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Primary Open-Angle Glaucoma

Karanjit S. Kooner

Definition

How Is Primary Open-Angle Glaucoma Defined?

Primary open-angle glaucoma (POAG) is a chronic, slowly progressive, multifactorial, usually bilateral, though not necessarily symmetrical, optic neuropathy. It is characterized by atrophy and cupping of the optic nerve head, resulting in a distinctive pattern of visual field defects, with or without elevated intraocular pressure (IOP), in the presence of a widely open angle and in the absence of other causes of damage to the nerve fiber bundles.[1]

Epidemiology and Importance

What is the Etiology of POAG?

The current treatments for glaucoma focus on lowering IOP. This approach may not be enough, as 25 to 38% of patients may continue to lose visual fields and develop blindness even when IOP has been reduced to the normal range.[2–4] Hattenhauer and associates'[5] research has suggested that 27% of glaucoma patients go blind in at least one eye after 20 years or more with the disease. It is well known that the underlying pathology in POAG is the death of retinal ganglion cells. The cells preferentially damaged in glaucoma are the magnocellular retinal ganglion cells.[6,7] Both experimental animal studies of the retina and human autopsy studies of lateral geniculate nucleus in glaucoma also point to the damage of larger retinal ganglion cells that project to magnocellular layers of the lateral geniculate.[8–10]

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The most prevalent theories attempting to explain glaucomatous optic neuropathy are the mechanical theory and vascular theory. In the mechanical theory the emphasis is on the damage to the optic nerve neurons at the level of the lamina cribrosa by the elevated IOP.[11] Alternately, the raised IOP may attenuate the sensitive microcirculation to the optic nerve head. On the other hand, the vascular theory suggests that eyes with inherently poor vascular supply to the optic nerve head are more predisposed to damage by elevated or normal IOP.[12] But the cause-and-effect relationship between nerve damage and vascularity has not been established. Sponsel and coworkers[13] discovered that in patients with glaucoma or ocular hypertension, the eye with the higher velocity of retinal leukocyte flow was associated with better visual function with regard to visual fields and contrast sensitivity. It is controversial whether increased blood velocity translates to enhanced perfusion pressure to a particular area. Further support for the vascular theory came after the development of the laser Doppler flowmetry (LDF) technique to evaluate the circulation of the optic nerve.[14] Studies have shown diminished blood flow in the optic nerves of eyes with POAG.[15,16] Similarly, optic nerve flow was decreased in patients with low systemic blood pressure and increased in patients with hypertension.[17] It is still doubtful whether LDF measures the entire blood flow to the optic nerve head, though most investigators believe LDF penetrates as far as the level of the lamina cribrosa.[18] As neither theory could explain all cases of glaucoma, the trend is to combine the two views together.

In the late 1960s and early 1970s another theory was proposed that elevated IOP might block axoplasmic flow at the lamina cribrosa.[19,20] The resultant interruption of trophic factors to the ganglion cell body might cause the cells to initiate a suicidal response resulting in programmed cell death or apoptosis.[6] The focus now has shifted more to understanding the response of nerve tissue to trauma and aging. Profiting from the data emerging from studies of central nervous system trauma and spinal cord injury, the new concepts of excitatory neurotoxins and apoptosis were applied to understanding the damage in glaucoma. When nervous tissue is severely injured, regardless of the cause, it follows the same common final pathway before neuronal death. The injurious events may relate to ischemia/hypoxia, trauma, hypoglycemia, stroke, and various acute or chronic degenerative and hereditary neuronal diseases.[21] The functional damage to the nervous tissue continues to progress even after the primary cause has been removed. These new concepts may help us understand why some glaucoma patients continue to exhibit progressive neuropathy even after an offending factor such as high IOP has been controlled. Moreover, there is evidence that up to 50% of retinal ganglion cell axons may be lost by the time visual field loss and abnormal cupping are detected.[22,23]

The term *secondary degeneration* has been applied to progressive neuropathy that spreads to adjacent areas far beyond the initially injured neurons. The aim of therapeutic neuroprotection is to protect these initially spared neurons from the ravages of secondary degeneration. The biochemical events surrounding the area of nerve injury involve the release of the excitatory amino acids glutamate and asparate. These amino acids have the ability to excessively stimulate the nerve and cause neuronal fatigue, toxicity, and ultimately nerve death.[24] The cytotoxic effects of glutamate on the inner layers of the retina are well known.[25,26] Dreyer and coworkers[27] also discovered significantly higher levels

of glutamate in the vitreous samples of glaucoma patients compared to normal individuals. Similarly, Brooks and coworkers[28] found significantly high vitreal glutamate concentration in dogs with primary glaucoma compared to normal animals. Even relatively minor but chronic elevation of glutamate may be toxic to the retinal ganglion cells.

After the release of glutamate at the injury site, Na^+ enters the cell. There is concomitant entry of chloride ions and water, causing cellular swelling. These events constitute the acute phase of neuronal trauma. Depending on the severity of the insult, the cell may recover or proceed to further loss of function and death. In the second or delayed phase there is cellular influx of Ca^{2+} and once the calcium homeostasis is altered a wide variety of abnormal biochemical reactions ensue. There is release of cytotoxic enzymes such as protease, endonuclease, and lipase that destroy cell membrane. Free radicals accumulate and further disturb the essential metabolic functions of the cells. Glutamate toxicity also releases G protein via its stimulation of metallotropic receptors, which in turn activate phospholipase C. The end result is major disruption of normal cellular function.

Another important pathway for cellular death is apoptosis. This active process is different from necrosis and when triggered by calcium ion imbalance enables the cell to die without liberating its digestive enzymes. Apoptosis appears to be controlled by genes, which might be altered to prevent the deadly program. Quigley and coworkers[6] have shown that ganglion cell death in glaucoma shares certain similarities with classic apoptosis. Retinal cells in glaucomatous optic neuropathy display chromatin condensation and involution or shrinkage. Neufeld and coworkers[29] have demonstrated increased levels of nitric oxide synthase (NOS) isoforms 1, 2, and 3 in the optic nerve head of patients with POAG. The presence of NOS-1 and -2 suggests that nitric oxide may reach toxic levels in the optic nerve in glaucoma. Excitotoxicity, even when mild, can cause neuronal apoptosis.[30] Excitotoxicity of retinal ganglion cells is mediated by overstimulation of a subtype of glutamate receptor, the *N*-methyl-D-asparate (NMDA). Dreyer and associates[31] have shown that agents that interfere with translation or transcription of these proteins are also effective in preventing NMDA-induced excitotoxicity. Overstimulation of NMDA receptors activates NOS, which mediates increased levels of nitric oxide and superoxide anion.

A new sequence of events leading to glaucomatous nerve damage has surfaced. The first stage may be triggered in susceptible patients by factors such as elevated IOP. In the second stage, damaged ganglion cell axons either come under the influence of neurotropin deprivation and/or release excitatory amino acids. With the loss of neurotrophic support of the ganglion cells, slow death is inevitable. There is also the consensus among the proponents that these events are interconnected and once initiated are hard to control with present-day therapy for glaucoma.

Hayreh et al[32] raised the issue of nocturnal hypotension in the development and progression of glaucomatous optic neuropathy. The physiologic drop in blood pressure at night, for example, may have adverse effects on a glaucoma patient with compromised optic nerve circulation. Hayreh's group[33] also prospectively investigated the effects of topical beta-blocker eyedrops on nocturnal blood pressure, heart rate, and visual field function. The study showed that in patients with normal-tension glaucoma, on beta-blocker therapy, there was a significantly more marked visual field progression (p =. 0003) than in

those not using topical beta-blockers. These patients also exhibited significantly greater decrease in mean diastolic blood pressure (p =. 009) at night compared to patients with ischemic optic neuropathy.

The age-dependent reduction in the number of optic nerve fibers is also an important consideration.[34] High-pass resolution and histologic studies have suggested the average loss of 10,000 nerve fibers every year after the age of 40 years. As the average number of nerve fibers is approximately 1.2 million, a person in his or her mid-80s may have lost approximately 40% of neurons, due to age-related events.

Is POAG Restricted to a Particular Geographic Area?

There is good evidence that POAG is a worldwide disease.[35] Some estimates suggest that at the end of the 20th century, over 60 million people were affected by glaucoma throughout the world and nearly 10% of those affected were blind bilaterally.[36] No race, community, or continent is immune from the disease. A large number of glaucoma-based epidemiologic studies have been conducted in different parts of the world and have yielded useful information, though they lack uniformity of design and definition of the disease.

The World Health Organization (WHO) Program for the Prevention of Blindness has tried to estimate the distribution of POAG based on the populations in nine different regions defined by the World Bank.[37] Of the total global POAG patient population, the percent distribution in the different regions is as follows: established market economies, 17.6%, former socialist economies of Europe, 7.2%; Latin America and the Caribbean, 6.7%; sub-Saharan Africa, 19.4%; Middle East/North Africa/southwest Asia, 5.2%; China, 20.1%; India, 12.9%; other Asian and Pacific countries (high income), 3.6%; and other Asian and Pacific countries (low income), 7.2%. Therefore, developing countries account for approximately 70% of the world's POAG cases.

In Africa, the majority of the population is black, with pockets of whites scattered throughout the continent. North Africans have Caucasian features. Due to various reasons and especially socioeconomic conditions in Africa, the prevalence of blindness is the highest in the world and rates of 3.6 to 5.2% have been reported.[37] In Ivory Coast, Ahnoux-Zabsonre et al[38] retrospectively reviewed charts of 33,000 patients attending a private clinic. There were 24,751 black and 8,249 white subjects. They found a prevalence of 2.1% in black and 0.75% in white patients. In both groups the prevalence rate increased with age. In black patients the mean age at detection of POAG was 46.4 ± 12.5 years, whereas it was 52.8 ± 12.2 years for white patients. Of the 571 patients with POAG, 38.5% had normal tension glaucoma. In an epidemiologic study in Cameroon looking at causes of unilateral blindness, Moussala et al[39] found POAG responsible for 22% of cases, following closely cataract and ocular trauma. Ouertani et al[40] examined all 856 individuals over the age of 40 years for POAG in one county of Tunisia and detected prevalence rate of 2.68%. They also found direct correlation between the prevalence rate and increasing age. The rate was 0.54% in subjects between 40 to 50 years, 1.71% in those between 51 to 65 years, and 50.63% in individuals over 65 years. Ninety-one percent of patients found to have glaucoma were unaware of the condition and 30.4% suffered from advanced disease. In the tiny nation of Togo, Balo and Talabe[41] noted that

66.87% of patients with POAG were under 45 years old; 65.12% were male and 34.88% were female. Optic nerve head cupping was significantly greater in the left eye compared to the right ($p < .02$). Glaucoma was responsible for 17% of blindness in 523 patients found to have visual impairment in the rural communities of Central Ethiopia.[42] Nwosu[43] conducted a 1-year study looking for new cases of blindness at a teaching hospital eye clinic in Anambra State, Nigeria. He found that of 257 patients with blindness, glaucoma was responsible for 22.2% of visual impairment in at least one eye. A community-based cross-sectional study in the Segou region of Mali examined 5,871 inhabitants of three rural districts.[44] Bilateral blindness rate was 1.7% and glaucoma accounted for 8.1% after cataract and trauma. The prevalence of POAG in central Tanzania during a survey of ocular diseases in adults was 3.1%.[45] The subjects were examined from six randomly selected eligible villages.

In contrast to the results of the above studies, the prevalence of POAG in South Pacific islanders is rare. During a trachoma survey in 1955, Mann and Loschdorfer[46] found only one case of POAG among 13,268 inhabitants of Papua, New Guinea.

Asia is populated by different races with varied facial features and skin color. India has a population of nearly a billion people and the WHO estimates that nearly 9 million inhabitants are blind, and that glaucoma may be responsible for 12.8% of the cases.[47] The Vellore Eye Survey was conducted in Vellore in South India, and examined 972 individuals between the ages of 30 and 60 years.[48] The prevalence of POAG, primary angle-closure glaucoma, and ocular hypertension were 4.1 (0.08–8.1), 43.2 (30.14–56.3), and 30.8 (19.8–41.9) per 1,000 inhabitants, respectively. The main drawbacks of the study were lack of subjects over the age of 60 years and a low response rate of only 50.3% from the eligible individuals. A similar population-based, cross-sectional study was carried out in the city of Hyderabad.[49] The investigators wanted to determine the prevalence and cause of moderate visual impairment. There were 2,522 total participants of all ages, with a high response rate of 85.4%. Primary angle-closure glaucoma and POAG accounted for 0.4% and 2.0% of moderate visual impairment respectively.

China is the world's most populated nation, with over a billion citizens. China is a relatively homogeneous society, and the prevalence of primary closed-angle glaucoma is greater than POAG. Hu[50] conducted an epidemiologic survey in Shunyi County of Beijing and found prevalence rate of 0.41% for primary angle-closure glaucoma and 0.11% for POAG. Both conditions were responsible for 9.28% of the blind and 16.67% of visually impaired patients. Compared to the glaucoma prevalence of 0.60% for the entire study population, the prevalence in subjects over 40 years was 1.40%. Another study in Tongcheng County of Anhui Province found a prevalence rate of 0.31% for primary angle-closure glaucoma and 0.07% for POAG.[51] The overall prevalence of glaucoma was 0.38%, whereas in individuals over the age of 40 years the rate was 0.71%. Gao et al[52] examined 331 patients with glaucoma at the Third Affiliated Hospital of China Medical College and 275 patients at the eye clinic of Kyushu University in Japan during a 2-year period. Glaucoma patients made up 1.5% of the 22,869 patients in the former institute and 1.8% of the 15,585 outpatients of the latter. At the China Medical College the distributions of the various glaucomas were primary angle-closure glaucoma (76.4%),

POAG (4.8%), secondary glaucoma (11.8%), and congenital glaucoma (5.7%). In comparison, the findings from Japan were primary angle-closure glaucoma (34.5%), POAG (12.7%), secondary glaucoma (22.2%), exfoliation glaucoma (14.9%), and congenital glaucoma (10.9%). A well-designed nationwide glaucoma survey was carried out in Japan under the auspices of the Japanese Glaucoma Research Club in 1988–89.[53] Of the 5,092 subjects evaluated, 1.6% showed IOP abnormalities, whereas 5.1% had optic disc changes. On further examination, prevalence of POAG was found to be 0.5% while 1.4% of the subjects were diagnosed with low-tension glaucoma.

The Melbourne Visual Impairment Project was a population-based study designed to assess the distribution and causes of eye diseases in Melbourne, Australia.[54] The investigators examined 3,271 residential subjects and 403 nursing home patients. The response rate was 83% for the former and 90.2% for the later. In the residential population the prevalence rate for POAG was 1.7% (95% confidence limits =1.21, 2.21). Nearly half of these participants were unaware of their disease. Primary angle-closure glaucoma was detected in two persons (0.06%), whereas six (0.2%) had secondary glaucoma. Age was a significant risk factor as the prevalence rate increased from 0.1% in people between 40 to 49 years to 9.7% in those between 80 to 89 years. A person's gender played an insignificant role. The prevalence rate for glaucoma in nursing home patients was 2.36% (95% confidence limits = 0, 4.88).

Bonomi et al[55] examined 4,297 persons (73.9% participation rate) in rural areas of northern Italy who were over 40 years of age. The investigators looked for ocular hypertension, POAG, primary angle-closure glaucoma, and normal-tension glaucoma, and found prevalence rates of 2.1%, 1.4%, 0.6%, and 0.6% respectively. In Western Scotland, Ghafour et al[56] analyzed blind registration forms of new 647 legally blind patients for the fiscal year 1980. Overall, glaucoma accounted for 14.6% of legal blindness and was the second most common cause behind senile macular degeneration (29.8%). In a geographically well-defined county in central Sweden, the investigators identified glaucoma population with the help of data from local hospitals and pharmacies.[57] The prevalence of glaucoma was 1.4% in individuals over 45 years of age.

The prevalence of glaucoma in Western developed countries was evaluated by Tuck and Crick.[58] They analyzed data from eight surveys and estimated prevalence rates for POAG in mainly white Caucasians 40 to 89 years of age to be 1.2%. This estimate ranged from 0.2% for individuals in their 40s to 4.3% for those in the 80s. The age distributions were 7% less than 55 years, 44% between 55 and 74 years, and 49% older. They also indirectly estimated incidence from the prevalence results (implied incidence), and calculated the rate to be 0.11% per year in persons between 55 and 74 years.

St. Lucia in the West Indies is home to a relatively homogeneous black population. The investigators used a cluster sampling method and examined 1,679 individuals older than 30 years.[59] The prevalence rate for glaucoma was high, being 8.8%.

How Common is POAG in the United States?

In the United States, glaucoma as a composite group is the second most frequently reported principal diagnosis at office visits to ophthalmologists after

cataract.[60] It makes up about 15% of all visits relating to illness or injury in ophthalmology. Among patients making return visits for the care of their previously treated eye condition, glaucoma accounted for about 20%. Among all the glaucoma-related office visits for the 2-year period of 1991–92, the diagnostic coding in descending order of frequency were unspecified glaucoma (63.2%), open-angle glaucoma (20.7%) and borderline glaucoma (14.0%). The open-angle glaucoma category was composed of POAG (10.7%), open-angle glaucoma, unspecified (9.2%), and other open-angle glaucoma (0.8%). In individuals 65 years and older, glaucoma was the third most commonly reported principal diagnosis. Although glaucoma accounted for 3.2% of all diagnoses in persons between 65 and 74 years of age, it was higher (4.4%) in persons 75 years and over. When comparing the principal diagnosis of glaucoma with all other ophthalmic and nonophthalmic diagnoses, it was the 13th most frequently mentioned condition. Glaucoma is also the second leading cause of legal blindness in America.[61] In African-Americans, however, it is the most common cause of blindness and visual impairment.[61] Of all adult glaucoma, POAG constitutes 60 to 70%. Approximately 80,000 Americans are blind from the disease, and 2 to 3 million have glaucoma.[62] As a majority of patients are asymptomatic during the early and intermediate stages of the disease, it is estimated that approximately half of the patients may be unaware of their disease.[63] Therefore, for physicians and government health planners alike, POAG poses a grave challenge. The population-based Baltimore Eye Survey examined 5,308 inhabitants of East Baltimore and discovered 161 (3.03%) cases of POAG.[64] In 1975, the Framingham Eye Study found a prevalence of 3.3% for POAG among 2,477 individual examined.[65]

Has There Been an Increase or Decrease in POAG Over the Years?

There is some evidence, that the prevalence (the number of cases of a disease in a defined population at a defined point in time) or the incidence (the number of new cases of a disease during a defined period of time) of POAG has increased over the years. The sampling data collected by the National Ambulatory Medical Care Survey (NAMCS) of the Division of Health Care Statistics of the National Center of Health Statistics, Centers for Disease Control and Prevention, has provided useful information.[60] In patients 65 years of age and older, between 1975 and 1992, glaucoma changed from being the ninth most mentioned morbidity-related principal diagnosis to the fifth. During 1975–76 there were 2.3 million glaucoma related visits and by 1991-92 the numbers showed a 284.6% increase to 8.7 million per year. Increased visit rates were observed in all age groups over 45 years. For example, in individuals 65 years of age and older, the rate for glaucoma visits increased from 5.7 visits per 100 subjects in 1975 to 19.9 visits per 100 subjects in 1992. These increased rates were observed in both sexes. According to the National Health Interview Survey (NHIS) individuals reporting a glaucoma-related condition increased from 5.7 conditions per 1,000 persons in 1977 to 10.4 conditions per 1,000 persons in 1991. Between 1982 and 1991, in persons 65 years and older, the reporting of a glaucomatous condition increased from 41.8 conditions per 1,000 persons to 57.8 conditions per 1,000 persons. However, more cases are

also being discovered nowadays because of factors like better detection methods, the aging population, and heightened public awareness. As glaucoma is a disease of the elderly who are now living longer because of better health care, we can expect to encounter more cases of glaucoma in the 21st century.

What Are the Demographic Characteristics of Patients with POAG?

There are several risk factors for developing POAG and not every patient has all the known risk factors (Table 2–1). While some factors appear to complement each other, there are several that may very well operate independently. It is well accepted that POAG is a disease of the elderly and the risk increases with aging.[65–67] This high prevalence in older populations may be explained on the basis of prolonged exposure to raised IOP or deteriorating microcirculation of the optic nerve head.

Several studies have demonstrated that increased IOP is associated with greater prevalence of POAG[63] and glaucoma-related visual field defects in established POAG patients.[68] This clinical observation is amply supported by experimental studies in primates and experience with treating patients with acute glaucoma.[69] In practice, however, patients show great variability in response to elevated IOP. Population-based studies have shown that only one-tenth or less of individuals with raised IOP will have accompanying glaucomatous visual field loss.[63] Longitudinal studies with ocular hypertensives have revealed that barely one-tenth of such subjects develop glaucoma over a ten-year period.[70] Normal IOP may be observed in almost one-sixth of well-established glaucoma patients even on repeated examinations.[63] Other deficiencies include the lack of a practical and economical means for monitoring 24-hour continuous IOP, or at least a reliable diurnal pressure. Zeimer and associates[71] reported that in some glaucoma patients, IOP may be elevated upon

Table 2–1. Risk Factors for POAG

Age over 40 years
Elevated IOP
African American ancestry
Family history of glaucoma
Ocular trauma
Topical, systemic, or endogenous corticosteroids
Myopia
Diabetes mellitus
Hypertension
Carotid vascular disease
Dysthyroid disease
Acute blood loss
Anemia
Vascular insufficiency
Migraine headaches

awakening but drop precipitously within half an hour. Thus, a physician may fail to gauge the true nature of pressure spikes.

Race is an important risk factor, and African-Americans are four to five times more likely to develop POAG than other races.[66,72,73] The disease also strikes them early and they usually present with severe damage at the first visit. Moreover, the glaucomatous process is more refractory to treatment and results in a higher rate of blindness.[66] It is estimated that one in 10 elderly blacks and one in 50 elderly whites have glaucoma. In the Barbados Eye Study, a population-based prevalence survey, IOP was significantly higher in the black participants compared to their white counterparts.[74,75] The mean values for the black and white individuals were 18.7 ± 5.2 mm Hg and 16.5 ± 3.0 mm Hg, respectively. Similarly, IOP greater than 21 mm Hg was present in 18.4% of blacks and 4.6% of whites. The prevalence of POAG in the black population was 7% and the odds of having IOP greater than 21 mm Hg was five times higher in this group. Conversely, examination of 2,773 Australian aborigines revealed no case of POAG.[76] The Health and Nutrition Examination Survey of 1971 to 1974 also found that black Americans had slightly higher IOPs than their white counterparts.[77] Mean IOPs of all groups increased with age, and there was positive correlation with systemic blood pressure.

A family history of glaucoma should always raise a red flag. Such a history may be found in 13 to 25% of glaucoma patients.[78] Both autosomal-recessive and -dominant transmission may be involved. Miller[79] examined 75 immediate descendents of patients with POAG between the ages of 15 and 60 years and performed tonography together with careful evaluation for glaucoma. The results showed that 8% had definitive POAG, 36% had suspicious outflow value, and 56% had no evidence of glaucoma. The average ages of the three groups were 48.5, 39.6, and 32.5 years, respectively. More recently in the Baltimore Eye Survey, the investigators calculated relative risk for developing glaucoma for a person with a sibling diagnosed with POAG to be 3.7-fold.[80]

Perfusion pressure is the difference between arterial pressure and venous pressure. IOP raises venous pressure at the exit point of the eye and thus affects intraocular blood flow. Decreased intraocular blood flow lowers perfusion pressure. Even normal IOP has an impact on the perfusion pressure, because it exceeds orbital venous pressure. Similarly, IOP induced ischemia can result from impaired autoregulation in a patient because of vasospastic disease, atherosclerosis, platelet or clotting abnormalities, and systemic hypertension.[81]

There is a well-known association of both systemic hypertension and hypotension in patients with glaucoma.[81–84] Many patients with POAG and normal-tension glaucoma exhibit elevated blood pressure.[85] Similarly, low systemic blood pressure is also a risk factor in glaucoma.[82,86] It is believed that chronic hypertension may cause ischemia, and low systemic blood pressure may reduce local perfusion of the optic nerve head, especially when the eye has elevated IOP or poor autoregulation.[87] Equally important is to understand the effect of physiologic nocturnal hypotension on the progression of glaucomatous field loss. Patients who exhibit greater nocturnal hypotension tend to show progressive field loss even at well-controlled IOP.

There is a close association between glaucoma and diabetes mellitus.[88] Clinically, diabetic patients show an almost threefold increase in the prevalence of POAG, elevated IOP, increased IOP response to topical steroids, and large

cup-to-disc (C/D) ratios as compared to nondiabetic individuals. The prevalence rate of diabetes in patients with glaucoma is reported to be 6 to 11%. On the other hand, glaucoma may provide a beneficial effect on the incidence of proliferative diabetic retinopathy. Patients with POAG and individuals exhibiting exaggerated IOP response to steroids both show increased prevalence of diabetes mellitus and positive glucose tolerance test. It is important to remember that both glaucoma and diabetes mellitus lead to blindness if undetected and untreated early on. Other common associated features of diabetes mellitus and POAG are hereditary components, tendency to produce eye damage over time, an asymptomatic nature, and the possibility of early detection.

Gender may be important, as some studies have found ocular hypertension more frequent in females and POAG more in males.[83,89] Myopia may coexist in 3 to 18% of patients with glaucoma.[90] The association between high myopia (>10 diopters [D]) and glaucoma is particularly significant ($p < .001$). Some of the high myopia-related factors implicated in the development of glaucoma are a structurally weak optic nerve in myopia, impaired aqueous outflow, choroidal vascular changes, strong familial tendency, and angle malformation. The Blue Mountain Eye Study, carried out in an Australian white community, found that glaucoma was associated with 4.2% of eyes with low myopia (> –1.0 D to < –3.0 D) and 4.4% of eyes with moderate to high myopia (> -3.0 D) compared to 1.5% of eyes with no myopia.[91] This two- to threefold risk of glaucoma in myopic subjects was maintained even when other risk factors and IOP were excluded.

Thyroid disorders are frequently associated with glaucoma. Cockerham and associates[92] reviewed charts of 500 patients with thyroid-associated orbitopathy and found that 120 (24%) had IOP greater than 22 mm Hg but less than 30 mm Hg. Of this group, 2% developed glaucomatous field defects over a follow-up period of 48 months. Several factors may cause raised IOP in patients with thyroid disorders, such as increased episcleral venous pressure secondary to orbital congestion, excessive mucopolysaccharide deposition in the trabecular meshwork, a direct thyrotoxic effect, or a genetic predisposition to glaucoma.

The Collaborative Glaucoma Study[93] conducted between 1960 and 1973 was a prospective study that examined 5,000 subjects in five centers for risk factors that may influence the development of POAG-like visual field defects. Such defects were seen in 1.7% of the eyes. But during a period of 5 years, 98.54% of eyes with initial pressure of less than 20 mm Hg showed no glaucoma-like visual field defects compared to 93.34% of eyes with pressures greater than 20 mm Hg. Significant variables relating to glaucomatous visual field defects were reduced outflow facility (C-value 0.186 vs. 0.250), age (54.56 vs. 44.13 years), IOP (19.83 vs. 16.74 mm Hg), cup-to-disc (C/D) ratio (0.33 vs. 0.24), and pressure increase after water drinking (2.72 vs. 1.43 mm Hg). The authors stressed the multifactorial nature of glaucoma.

Are There Any Immunologic Factors Important in POAG?

Several immunologically based diseases such as rheumatoid arthritis, thyroid disturbances, migraine and Raynaud's phenomenon are seen in patients with POAG. Wax and coworkers[94] have found serum antibodies to retinal proteins

and retinal immunoglobulin deposition in an eye with glaucoma. Similarly, an immunologic basis of glaucoma was also suggested by David and coworkers,[95] who found an association of human leukocyte antigen HLA-DR3 allele in Caucasian patients with glaucoma. But a Spanish study found a frequency of HLA-DQA1 alleles similar in both patients with POAG and the controls.[96] However, the study showed the association of POAG with other genetic markers such as acid phosphatase ACP*C alleles located at the chromosome 2p23. Recently Gil-Carrasco and associates[97] detected haplotype HLA-DRB1* 0407-DQB1*0302 among Mexican Mestizo patients with POAG. They suggested that this haplotype with the disease may be the result of linkage disequilibrium or the influence of a neighboring gene.

Do Any Social and/or Economic Factors Contribute to Developing POAG?

Apart from black race, no socioeconomic, education, or occupation factor appears to have any significant effect on the prevalence of POAG. Once the disease is established, all the aforementioned factors become crucial depending on the patient's ability to pay for the doctor visits and medications, access to health care, and understanding of the disease process.

Are There Any Genetic Considerations for POAG?

There is a strong familial association in POAG.[98] The disease does not appear to follow any set familiar pattern, but a history of POAG in close relatives is much more significant than in distant relatives. Paterson[99] examined 50 siblings of patients with POAG and detected the disease in 8%. Out of 125 patients suffering from POAG, Biró[100] found that 16 (12.8%) were hereditary in nature.

The discovery of defective genes is an important milestone in the pursuit of early diagnosis and cure. It is essential to understand the genetic nomenclature of glaucoma in order to follow the recent advances and discoveries. To simplify the matter, glaucomas have been classified into POAG, primary closed-angle glaucoma, and congenital glaucoma. The corresponding prefixes for glaucoma loci are GLC1, GLC2, and GLC3. As new loci are discovered they are given an alphabetical letter after the GLC prefix. The first two genetic loci discovered for POAG were named GLC1A and GLC1B. Of the current eight genes or genetic regions assigned to GLC nomenclature, six relate to POAG, GLC1A–F, and two to congenital glaucoma, namely GLC3A–B. In 1993, Sheffield et al[101] mapped the GLC1A region to chromosome 1q21-q31 and the group later narrowed the region to a 3-cM region between the markers D1S3665 and D1S3664 in juvenile open-angle glaucoma patients. The mutated gene was identified as myocilin by Stone et al[102] in 1997. Escribano et al[103] had earlier isolated myocilin or trabecular meshwork-induced glucocorticoid response protein (TIGR) from the ocular ciliary body. The TIGR gene is made up of three exons and is capable of encoding a 501 amino acid chain protein. The third exon has been identified as the site of all glaucoma-related mutations. Yokoe and Anholt[104] found that the amino acid sequence encoded by the third exon was homologous to the frog olfactomedin gene and may form multimers. Wirtz and

coworkers[105] were successful in mapping a sixth gene for POAG, GLC1F, to 7q35-q36 in a family with a strong family history of glaucoma.

Is Community-Based Screening for POAG Helpful?

The detection and diagnosis of POAG in population-based studies is not easy. Screening surveys that do not include applanation tonometry, dilated fundus evaluation, and automated visual field examination are apt to miss significant numbers of patients. The value of IOP measurement may vary according to the time of the day as both intraday and interday fluctuations are well recognized.[106] Approximately one-sixth of all POAG patients may show IOP levels below 22 mm Hg consistently during population-based studies.[63] At a single screening, almost one-third to one-half of the patients with POAG may show pressures below 22 mm Hg.[107] On the other hand, not all patients with high pressures have glaucoma or will develop glaucomatous optic nerve damage.[63] Optic disc examination by direct ophthalmoscopy also has interobserver and intraobserver variations.[108] Visual field testing, though very useful, has its own drawbacks such as time required for testing and short-term or long-term fluctuations. At a public glaucoma screening, Yamada et al[109] found frequency-doubling technology perimetry superior to Damato campimetry. The former targets larger optic nerve fibers in the magnocellular pathway, which are selectively affected in early glaucoma.[7] Glaucoma screenings in general are quite useful but cumbersome and time-consuming. It is now recommended that it would be more economical to target at-risk populations, such as subjects over 40 years of age, African-Americans, and the elderly.

How Common Is Blindness in POAG?

In the United States there is no central agency for blindness registration. Therefore, we can only estimate the number of blind individuals. The definitions of legal blindness and visual impairment are also not standardized worldwide and therefore pose difficulties in comparing their prevalence. Legal blindness in North America is defined as best corrected visual acuity of 20/200 or less or a visual field of less than 10 degrees in the better eye. The WHO defines blindness as visual acuity of less than 3/60 (0.05) or corresponding visual field loss in the better eye with best possible correction.[47] Visual impairment corresponds to visual acuity of less than 6/18 (0.3) but equal to or better than 3/60 (0.05) in the better eye with best possible correction. It is estimated that 71% of blindness in the world is from three conditions: cataract, trachoma, and glaucoma. Approximately three-fourths of all blind individuals reside in Africa and Asia. The estimates by WHO suggest that depending on geographic location, glaucoma is responsible for 5.7 to 22.7% of all blindness worldwide. It may be fair to estimate that around 10% of global blindness may be from glaucoma. The country with the largest percent of glaucoma-related blindness is China, where more than half of the world's patients with POAG are believed to reside. In the United States, the estimate for legal blindness from glaucoma is 16.2 cases per 100,000 population.[110] Most experts believe that these data underestimate the real problem by two- to threefold because of underreporting of blindness in the country.

How Much Does the General Population Know About Glaucoma?

The knowledge about glaucoma is quite scanty in the general population. In Germany, Pfeiffer and Krieglstein[111] surveyed 2,600 men and women over the age of 14 years. Only 30.0% of the subjects had heard about glaucoma. The awareness was greater in individuals who wore glasses or contact lenses (44.0%). The symptoms believed to be associated with glaucoma were blurred vision (39.0%), pain (28.0%), and difficulty in reading (22.0%). Approximately 11.0% knew that there were few subjective symptoms in glaucoma while 29.0% thought they would be able to feel elevated IOP. Two factors responsible for poor vision were believed to be excessive reading (16.0%) and smoking (11.0%). Therapeutic measures mentioned for glaucoma included surgery (63.0%), laser treatment (26.0%), and medications (23.0%). The sources of glaucoma information were friends (44.0%), doctors (13.0%), and opticians (2.0%). There was little correlation between knowledge of glaucoma and a person's education, profession, and income.

Does Glaucoma Reduce Life Expectancy of Patients?

Several studies have looked at the question of adverse effects of glaucoma on life expectancy of persons with glaucoma.[112,113] Hiller and associates[114] used data from the Framingham Eye Study and Framingham Heart Study to see if raised IOP or a history of treatment for glaucoma is associated with decreased survival. They divided patients into three groups: low pressure (<20 mm Hg), medium pressure (20–25 mm Hg), and high pressure (> 25 mm Hg). The death ratio for the group with medium IOP relative to the group with low pressure was 1.04. The group with high pressure had a corresponding death ratio of 1.56. The data suggested that high IOP or presence of glaucoma is a marker for decreased life expectancy.

Diagnosis and Differential Diagnosis

What Are the Presenting Symptoms of POAG?

There may be no symptoms or the patient may present with nonspecific symptoms (Table 2–2). These patients may visit an ophthalmologist as part of a routine eye checkup or in relation to some symptom of an ailment such as diabetes mellitus, hypertension, thyroid dysfunction, anemia, or some cardiovascular function.

Table 2–2. Presenting Symptoms of Patients with POAG

Asymptomatic
Blurry vision, decreasing vision
Ocular pain
Difficulty driving, especially at night
Frequent change of glasses

What Are Some of the Most Pertinent Questions to Ask the Patient?

Once glaucoma is suspected, the comprehensive evaluation should relate to present or past ocular history, family and social history, medical history, use of topical and/or systemic drugs, and any drug allergies. Rule out local or systemic contraindications to the use of glaucoma medications such as certain cardiovascular, bronchospastic, central nervous system, and renal disorders. For example, the physician may want to avoid topical beta-blockers in patients with asthma, and carbonic anhydrase inhibitors in patients with history of renal stones.

How Is a Patient with POAG Evaluated?

After a complete history one needs to know the status of the best corrected visual acuity. Some patients may notice a dramatic drop in their vision for the first time after the good eye is covered. Pupillary reflexes should be checked to rule out subtle or early relative afferent pupillary defect. Other steps are described below.

Is IOP Elevated in All Patients?

As previously mentioned, not all patients exhibit elevated IOP at all times. The term *normal tension* or *low-tension glaucoma* is reserved for patients who never show raised IOP. This does not mean that IOP stays normal at all times in these patients. It may be rising at certain times of the day, and this observation has prompted some to recommend diurnal or serial tonography. Alternatively, IOP may be checked at different times of the day on different visits. Goldmann-type applanation tonometry is preferred for standardized testing. Time of the day should always be recorded for diurnal comparison in the future. IOP is influenced by both physiologic and pathologic factors, and it is always prudent to perform multiple pressure measurements over a period of days or weeks to better assess the patient's pressure status. The average diurnal variation of IOP is approximately 6 mm Hg, and patients with glaucoma may exhibit variations of up to 30 mm Hg.[115]

Why Is Gonioscopy Essential?

A careful evaluation of the anatomic angle helps to exclude patients with narrow angles, angle closure, or other secondary forms of glaucoma. Excessive pigmentation may suggest trauma, pigment dispersion, pigmentary glaucoma, pseudoexfoliation of the lens, or intraocular tumor. Prominent angle recession may explain unilaterally elevated IOP. In an obviously quiet eye, it is important to rule out any prior use of topical corticosteroids.

How Should the Optic Disc and Nerve Fiber Layer Be Examined?

A critical part of glaucoma evaluation, the posterior fundus including the optic nerve head, is ideally examined through a dilated pupil.[116] The use of a slit-

Table 2–3. Other Causes of Glaucomatous-Type Visual Field Defects

Tilted disc
Disc drusen
Optic pits and other congenital defects
Retinal or choroidal diseases

lamp biomicroscope and a magnifying aid allows a stereoscopic evaluation.[117] Periodic stereo photography provides a more practical and inexpensive objective follow-up of the status of the optic nerve head. The nerve fiber layer may be evaluated by using red-free illumination from a direct ophthalmoscope or a biomicroscope. The posterior fundus should be carefully examined to rule out other causes of glaucoma-like visual field defects (Table 2–3). The new nerve fiber analyzers using scanning laser or confocal laser provide more objective evaluation of the optic nerve head.[118,119] Thus, interobserver and intraobserver errors are excluded.[108,120] Three-dimensional computer assessment of the optic disc has taken disc evaluation one step closer to a perfect objective test.[121] If these facilities are not available, then a detailed description and drawing of the optic disc or a mono-photograph should suffice.

The changes on the optic nerve head are not similar in all types of glaucoma, and glaucomatous eyes may lose retinal nerve fibers before clearly visible changes on the disc are evident.[122] After evaluating the size and shape of the disc, attention is directed to the surface of the nerve head. Compared to focal nerve damage, it is more difficult to diagnose diffuse nerve fiber loss. The characteristics of glaucomatous optic nerve damage are enumerated in Table 2–4. The C/D ratio should be noted in both the horizontal and vertical meridians. A vertically oval cup in the absence of a vertically elongated disc, C/D disparity of >0.2 between the eyes, notching, thinning of neuroretinal rim, and optic disc pallor in the presence of hemorrhage are some of the salient features of glaucomatous damage. Peripapillary atrophy or choroidal sclerosis and thinning of the retinal arterioles may be signs of ischemia. In a patient with POAG, splinter hemorrhage on the disc may be accompanied by a new nerve fiber bundle defect.[123] Disc hemorrhage may represent an acute ischemic event and is seen more frequently in patients with systemic hypertension.

Table 2–4. Characteristics of Glaucomatous Optic Nerve Damage

Asymmetrical cupping
Vertically oval cup
Generalized enlarged cup
Thinning or notching of the disc rim
Disc hemorrhage
Peripapillary atrophy
Baring of lamina cribrosa
Nasalization of optic nerve head blood vessels
Thinning of disc arterioles
Baring of circumlinear blood vessels

Four different types of glaucomatous optic discs have been described in glaucoma. The focal glaucomatous disc is characterized by localized neuroretinal rim loss at the inferior and/or superior pole of the optic nerve head.[124] With progressive deepening, the lamina cribrosa becomes exposed and is called laminar dot sign. There is a close correlation between the enlarged cup volume and glaucomatous visual field loss.[125] Associated peripapillary atrophy is also quite common. Myopic glaucomatous discs are tilted with a shallow appearance, a myopic temporal crescent of peripapillary atrophy, and thinning of the superior and/or inferior neuroretinal rim in the absence of signs of degenerative myopia.[126] Senile sclerotic or atrophic glaucomatous optic discs show diffuse neuroretinal rim tissue loss.[127] There is an associated complete ring of peripapillary atrophy and choroidal sclerosis. Eyes with generalized enlargement of the optic disc cup are characterized by enlarged round cups with no localized areas of neuroretinal rim loss or pallor. The majority of patients with glaucoma, however, tend to exhibit signs of two or more disc types.

Detection of optic nerve fiber damage is central to the diagnosis of POAG. It is also believed that damage to the optic nerve head occurs ahead of any recognizable change in the visual fields.[122,128] An optic nerve head with a large cup is also more susceptible to raised pressure as compared to an eye with a small or no cup. Larger cups may be associated with higher levels of IOP. Iester and Mikelberg[129] found no morphometric differences between high-tension glaucoma and normal-tension glaucoma patients as measured by scanning laser ophthalmoscopy. In patients with advanced glaucomatous optic atrophy, factors responsible for progressive visual loss are elevated IOP and noncompliance with treatment.[68]

How Should the Visual Field Be Evaluated?

The visual field is measured by the automatic static threshold method or by employing carefully the manual combined kinetic and static threshold technique. In cooperative patients, a fair amount of field defects may be detected by a quick confrontation method. There are a number of well-recognized field defects seen in glaucoma patients regardless of the type of the disease[130] (Table 2–5). These defects are the consequence of damage to the nerve fiber layer of the retina. The earliest changes may appear in the paracentral area in the form of decreased sensitivity or scotomas. The latter may be relative or absolute in nature. If the patient has developed a notch on the nerve head, it may be possible to predict the location of the field defect. As the disease progresses, the scotomas coalesce to form an arc-shaped defect often called arcuate scotoma. A nasal step may appear superiorly or inferiorly and is a frequent finding. An

Table 2–5. Characteristic Glaucomatous Field Defects

Arcuate defect
Nasal step
Paracentral scotoma
Generalized depression
Altitudinal defects

arcuate scotoma and a nasal step may join to form a much larger defect ultimately appearing as an altitudinal defect. In glaucoma there is usually a spillover to the other half of the field, in contrast to the neat bisection seen in central nervous system lesions. There is a well-accepted concept of localized and diffuse loss in glaucoma.[131] The former includes arcuate and paracentral defects, while the latter manifests as a reduction in sensitivity over the whole visual field. The localized loss is attributable to normal IOP, whereas the diffuse loss appears to be associated with high IOP.[132]

Most patients find visual field testing quiet frustrating and cumbersome. It is therefore crucial for the physician to spend some time explaining the procedure and its importance. An experienced and competent technician can play an important role in alleviating the fears of the patient. The patient's refractive error should be corrected and an appropriate reading is essential. Miotic pupils should be dilated with the same mydriatic agents each time and the pupil size measured. The visual field changes from small pupils and the interference from the rims of corrective lenses may complicate an already difficult situation.

Is Electrophysiologic Testing Helpful in Glaucoma?

Various electrophysiologic tests have proved not very helpful in glaucoma. For instance, luminance or standard-flash electroretinogram (ERG) is altered only in advance glaucoma.[133] Pattern ERG (PERG) has been found to be abnormal in several studies in patients with glaucoma, but the abnormalities do not match with other psychophysical test results in glaucoma.[134] The pattern visual-evoked potential (PVEP), on the other hand, is abnormal only in half of the patients with glaucoma.[135] Graham and coworkers[136] have used multifocal PVEP to determine visual field loss in glaucoma. In their study involving 43 glaucoma patients, the bipolar PVEP corresponded well with Humphrey visual field defects.

How Is a Patient with POAG Diagnosed?

A patient with POAG may present with any one or more of these prominent features: (1) elevated IOP, (2) increased cupping and atrophy, and (3) glaucoma-like visual field defect.

(1) How Should a Patient with Elevated Pressure Be Evaluated?

A patient may present with raised pressure in one or both eyes (Fig. 2–1). A majority of patients with elevated pressures show an inequality of values in both eyes or even relatively normal pressure in one eye. Sometimes one eye may show a lag period of several months to several years before the IOP starts to rise.

What Are the Gonioscopic Features?

The iridocorneal angle is moderate to wide open and all the angle structures are prominent. If the angle is narrow or closed the patient should be accord-

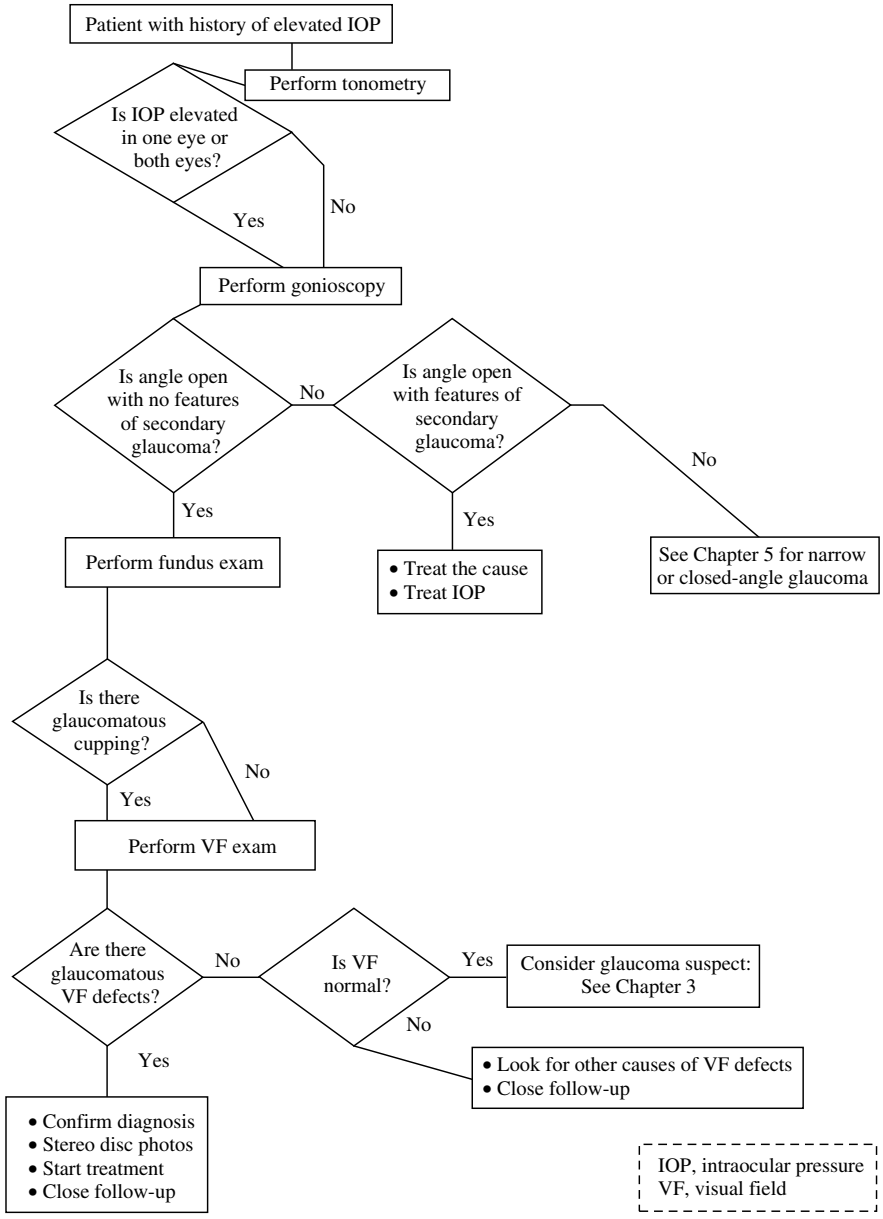

Figure 2–1. Management of a patient who presents with elevated IOP.

ingly managed (see Chapter 5). A patient may have angle recession in one or both eyes, and a history of ocular trauma is useful (see Chapter 13). This is also an opportunity to rule out other causes of raised IOP such as pigmentary glaucoma, pigment dispersion, inflammatory membranes and deposits, foreign bodies, anterior segment inflammation, and intraocular tumors. If there are features of raised episcleral pressures present then the management is different (see Chapter 6).

Is There Glaucomatous Cupping?

The changes on the optic nerve head should be carefully evaluated and compared with the other eye. If the optic disc changes are asymmetrical then there should be a very high suspicion for glaucoma. Occasionally, the disc features may suggest glaucomatous damage but still appear symmetrical. In such a situation visual fields and other risk factors would help to rule out physiologic cupping or congenital deformity of the optic nerve disc.

Are There Glaucomatous Field Defects?

In most patients visual field examination is most crucial. If the fields are normal in both eyes, then the patient may have any of the three diagnoses depending on the IOP, optic nerve head, and risk factor: glaucoma suspect (ocular hypertensive), physiologically large cups, or congenital deformity of the optic nerve head. When there are typical glaucomatous field defects in one or both eyes, then the glaucoma diagnosis is more likely as long as the IOP and optic nerve head features support the clinical impression. All efforts should be made to rule out conditions that may mimic glaucomatous field defects as discussed previously.

(2) How Is a Patient with Increased Cupping and Optic Atrophy Evaluated?

The features of glaucomatous optic nerve damage have been discussed before, and all other conditions that may simulate glaucomatous damage should be ruled out. A patient may show signs of damage in only one eye and this should alert the clinician to exclude secondary causes of unilateral nerve damage such as congenital deformity, trauma, inflammation, space-occupying lesions, and past or present use of topical corticosteroids (see Fig. 2–2).

Is the IOP Normal or High?

Careful measurement of IOP may reveal normal, low, or raised pressure in one or both eyes. A single pressure reading is noncontributory and may have to be repeated at different times of the day. Elevated IOP aids in the diagnosis but a normal or low pressure does not exclude glaucoma.

What Does Gonioscopy Reveal?

Gonioscopy is an essential step in the evaluation of patients manifesting suspicious optic disc changes. A closed angle may suggest primary or secondary angle-closure glaucoma and the management is discussed in Chapter 5. A patient exhibiting signs of narrow angle may be harboring combined mechanism glaucoma or impending angle-closure glaucoma, or may be a glaucoma suspect. If the iridocorneal angle is open, then the list of differential diagnosis is long. This individual may have POAG, low-tension or normal-tension glaucoma, ocular hypertension, secondary glaucoma, physiologic cupping, or congenital optic nerve deformity. The next step is evaluation of the visual fields.

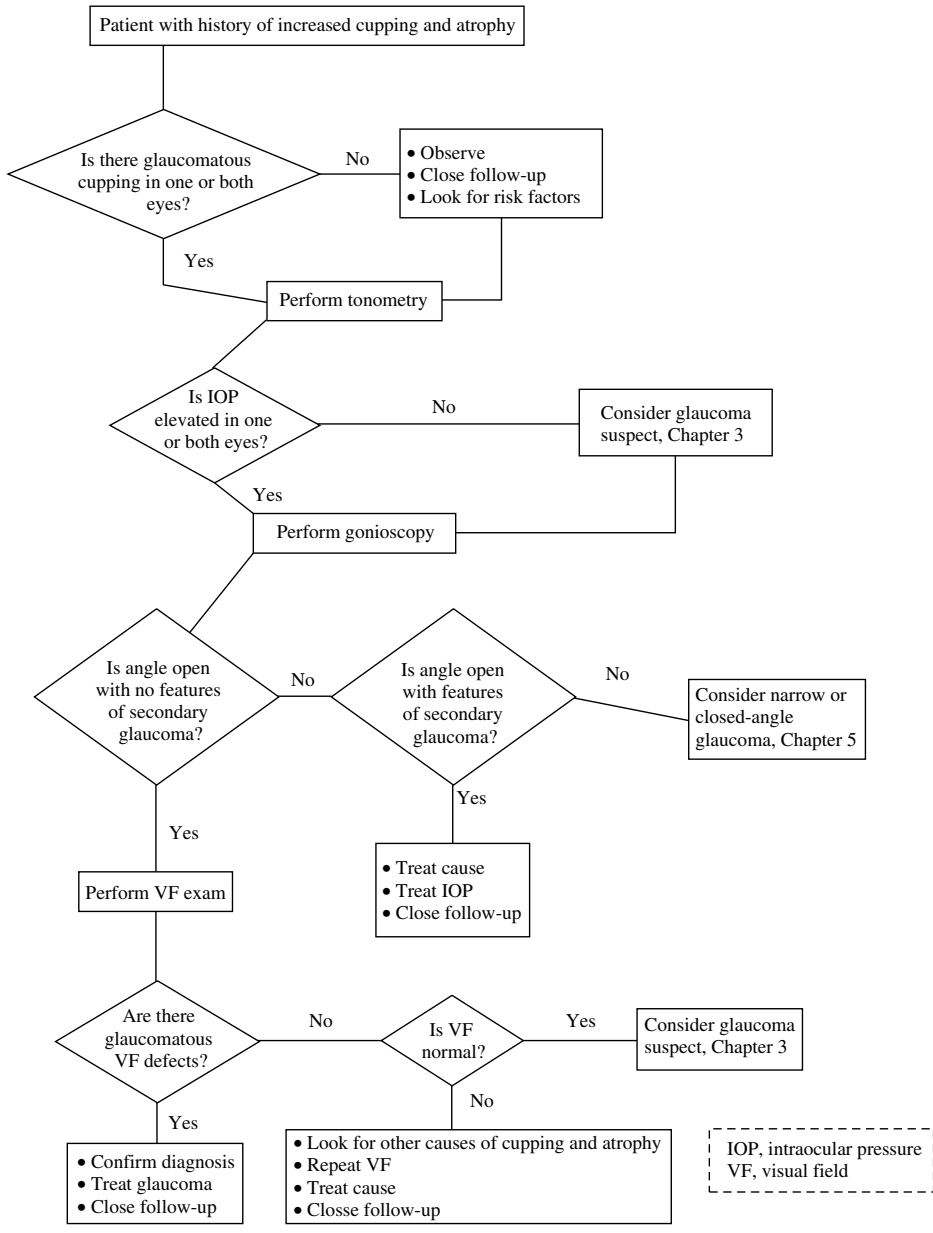

Figure 2–2. Management of a patient who presents with history of increased cupping and atrophy.

Are the Visual Fields Normal or Abnormal?

The visual field examination may reveal characteristic changes in one or both eyes but may also be normal in both eyes. In the latter situation, one has to consider ocular hypertension, physiologic cupping, and/or congenital deformity. A patient with glaucomatous visual field defects in one or both eyes and nor-

mal pressures may harbor normal- or low-tension glaucoma. On the other hand, a patient with typical glaucomatous field defects in one or both eyes and high IOP needs to be carefully evaluated for secondary causes of elevated pressure before a diagnosis of POAG is established.

(3) How Is a Patient Who Presents with Glaucomatous Visual Field Defects Evaluated?

It is not uncommon that a diagnosis of glaucoma is initially entertained when a patient shows suspicious field defects during the course of some other ocular investigations. If in doubt, the visual fields may be repeated to rule out short-term or long-term fluctuations in patient responses. The glaucomatous field defects may be unilateral or bilateral and one should rule out other causes of glaucoma-like field changes (Table 2–2). The next step is to check ocular tensions (Fig. 2–3).

How Are the Ocular Pressures?

The IOP may be elevated in one or both eyes and a record of past pressures would be very helpful to better understand the range of IOP fluctuations. In any case, knowledge of the status of the iridocorneal angle would be very helpful.

What Does Gonioscopy Reveal?

The iridocorneal angle may be open, narrow, or closed. The last condition should point to both primary and secondary types of angle-closure glaucoma. Similarly, an open-angle should suggest either POAG or other varieties of secondary open-angle glaucomas. A patient with narrow angles may present some difficulty in categorizing and usually needs careful follow-up and evaluation. Finally, fundus examination should help us to narrow in on the ultimate diagnosis.

What Does the Fundus Examination Show?

A thorough evaluation of the optic nerve head includes looking for signs of glaucomatous changes and any differences in the extent of damage between the two eyes. Though asymmetrical cupping is quiet common in POAG, symmetrical damage does not rule out the diagnosis. The final diagnosis should be made taking all pieces of information together.

Treatment and Management

The treatment and management of a patient with POAG poses a great challenge for the physician. Like many other chronic diseases, POAG may cause havoc to the mental, physical, economical, and social well-being of the patient. It is essential, therefore, to mentally prepare the patient while the investigations are progressing. After the diagnosis is confirmed and the initial status of

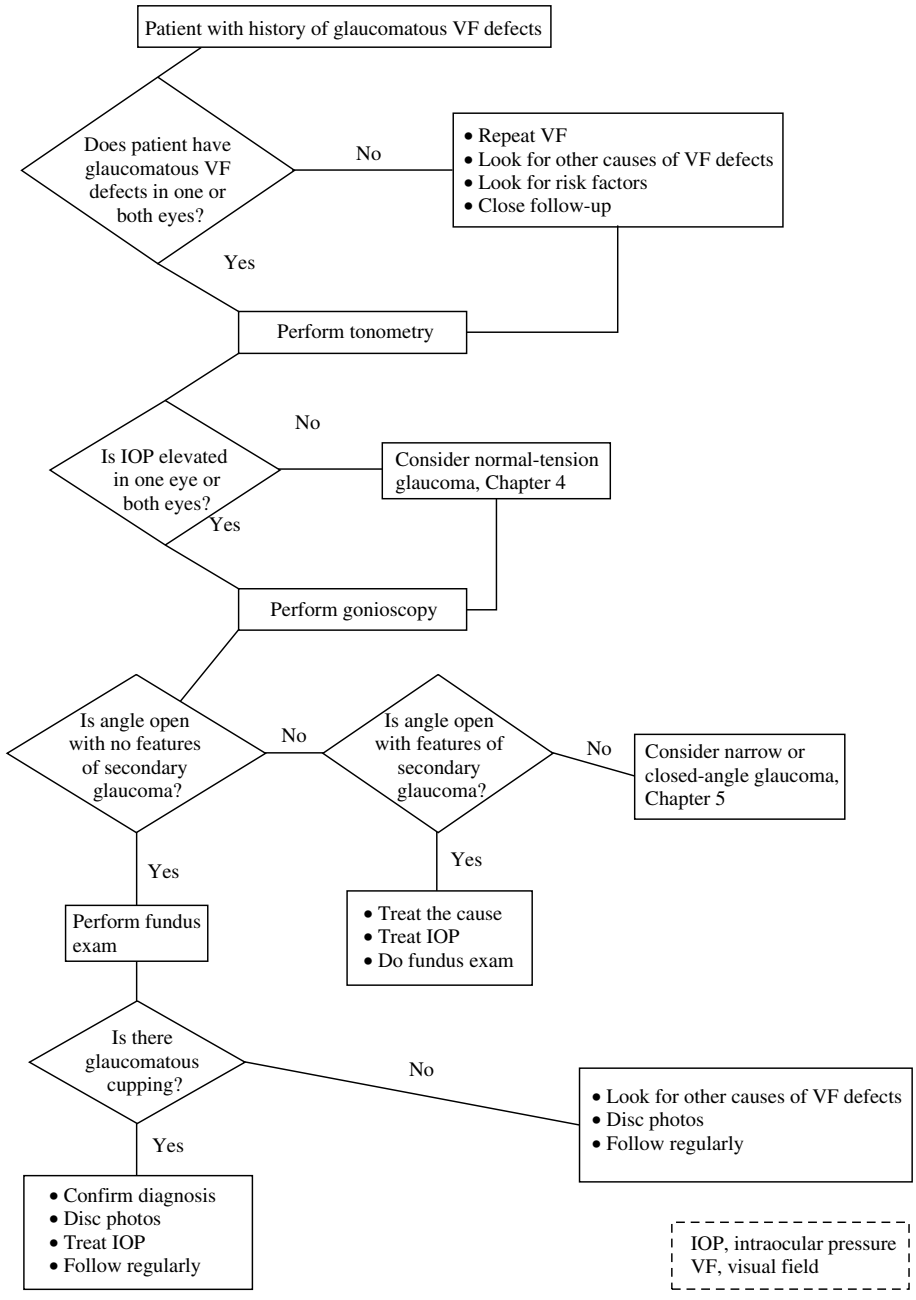

Figure 2–3. Management of a patient who presents with history of glaucomatous visual field defects.

the optic nerve structure and function is documented, it is time to break the news to the patient. Many physicians find it helpful if a family member is also present at the discussions. The physician should emphasize the lifelong commitment to therapy and follow-up. Different therapies, including topical and

systemic medications, lasers, and mechanical surgeries, should be explained. An estimate of the target pressure should also be a top priority as the therapy is begun, and henceforth all efforts are focused to maintain IOP at that level or below. The beneficial effect of reduced IOP on progression of glaucomatous damage is well documented.[137,138]

What Is the Initial Therapy of POAG?

This depends on multiple factors such as the height of IOP, extent of disease damage, age, local and systemic contraindications to therapy, social support, and mental status of the patient. If the IOP is very high (e.g., >35 mm Hg) it may be appropriate to begin with more than one medication. Otherwise, it is best to add one medication at a time. In this way, not only the response of therapy but also the dosage and side effects of each drug can be evaluated. To minimize diurnal effects on the IOP, many clinicians advocate monotherapy when considering additional topical therapy.

What Is the Definitive Treatment for POAG?

It may take months before the most appropriate combination of drugs is found. Chapter 18 provides a detailed description of individual drugs used to treat glaucoma, and Chapter 19 discusses various surgical procedures employed in managing the disease. The first agent of choice for most clinicians is still a beta-blocker. Both selective and nonselective agents are available. The chief contraindications are restrictive airway disease, bradycardia, and cardiovascular compromise. For the second position agent, one may choose between a prostaglandin analogue and an α-agonist. Latanoprost is the only prostaglandin analogue available and is very effective in reducing IOP, presumably by increasing uveoscleral outflow. The long-term side effects are still not known. Alphaclonidine and brimonidine are the two α-agonists currently available in the United States, and their long-term use is marred by a high degree of associated allergic conjunctivitis. If two different agents are unable to control IOP, some clinicians may consider argon laser trabeculoplasty next over adding another drug. The main considerations are noncompliance by the patient and the inability to bear the higher cost of medical therapy. For the third-agent spot, there is a choice between a topical and an oral carbonic anhydrase inhibitor (CAI). The two topical CAIs are dorzolamide and brinzolamide. Local allergies for both the agents are a concern for long-term use. Systemic CAIs are acetazolamide and methazolamide; the former also has a parenteral form. Oral therapy is associated with untoward systemic effects such as nausea, weakness, dizziness, insomnia, renal stones and skin rashes. The remaining antiglaucoma drugs are the miotics and epinephrine or its derivatives. Miotics are inexpensive but are associated with side effects such as miosis, ciliary spasm, myopia, and cataract formation, and noncompliance is a problem. Epinephrine-type drugs may cause annoying local irritation, headaches, elevated blood pressure, and cystoid macular edema in aphakes.

Argon laser trabeculoplasty is an effective way of reducing IOP. The advantages include its effectiveness and that it is performed in the office under topical anesthesia only. The availability of apraclonidine has reduced the chances

of transient postoperative pressure spikes. The disadvantages are a lack of long-term control and ineffectiveness in young adults.

A number of other surgical procedures are employed for uncontrolled glaucoma, namely trabeculectomy with or without antimetabolites, setons, and various cyclodestructive procedures (see Chapter 19).

What Is a Target Pressure?

Target pressure refers to an arbitrary range of pressure that a treating physician may feel is unlikely to cause further damage to the optic nerve.[139] As is obvious from the definition the pressure may vary from patient to patient and even in the same patient over the course of the disease. The minimal pressure that a clinician may try to achieve initially is reduction by 25 to 30%. Later the target pressure depends on variables such as age, race, degree of glaucomatous damage, compliance, and associated systemic ailments. The target pressure therefore, is an ever-changing number that the physician and patient both try to achieve with reasonable means. As a rule of thumb, the greater the damage, the lower the initial target pressure. It is always important to remember that there are factors other than pressure alone that may be responsible for glaucomatous damage.

How Common Is Noncompliance in Patients with Glaucoma?

Patient compliance with medications is an important challenge faced by all physicians. The close relationship between poor patient compliance to either medical or surgical therapy and progressive glaucomatous visual loss is well established.[68,140] It is such a complex problem that new noncompliance reasons are being confronted every day. In glaucoma patients some of the well-known reasons for noncompliance are lack of awareness of the severity of the disease, cost of medications, side effects of therapy, and helplessness under deteriorating visual status. Various helpful techniques that may help compliance include patient education, tailor-made topical therapy, family involvement in the management of the disease, support groups, and constant encouragement. The time spent in confronting noncompliance is well spent, as studies have shown that one-third or more patients do not take their medications as prescribed.[141,142]

What Is the Follow-Up Schedule for Patients with POAG?

The follow-up schedule should be tailor-made for individual patients. Apart from the level of control and severity of glaucomatous damage, other factors that may influence a patient's follow-up visits include noncompliance and degree of family/social support. It is essential to inquire about side effects of therapy, measure visual acuity, check IOP, and examine the optic nerve at each visit. Visual field evaluation and gonioscopy should also be done periodically. A patient with uncontrolled IOP and/or deteriorating optic nerve may have to be seen every day or weekly until the condition is stabilized. After adequate control, the visits may be increased to every 1 to 4 months. A compliant, stable patient may need to

be seen only two to three times a year. A visual field examination and optic nerve photography/imaging may be performed one to two times yearly.

What Is the Cost of Glaucoma Medications?

Whenever initiating medical therapy or changing medications, it is worthwhile to consider the cost of drugs. This is all the more important because most patients with glaucoma are elderly, on fixed income, and may be taking several other drugs concurrently. Several studies have looked at the question of the cost of glaucoma medications.[143,144] In 1999, Fiscella and coworkers[145] calculated daily patients cost of glaucoma medications. The costs per day for various drugs were beta-blockers $0.30 to $0.81, brimonidine $0.90, and latanoprost $0.92, respectively.

Is There Any Information Available Regarding Characteristics of Office Visits by Glaucoma Patients?

The data collected by the NAMCS have provided useful sampling information on various aspects of office visits by glaucoma patients.[60] In the most recent 2-year survey report of 1991–92, there were 17.5 million visits made by patients who were listed with the principal diagnosis of glaucoma. This translated to an average of 8.7 million visits per year or 3.5 visits per 100 persons per year. The visit rate for persons 75 years of age and over was considerably higher, being 26.8 visits per 100 persons. Moreover, during the same period 3.2 million more visits were by patients with glaucoma as their secondary or tertiary diagnosis. As would be expected, 92.8% of glaucoma visits were made by individuals at least 45 years of age, but over 61.3% of all patients were female. The average visit rate for females was 4.2 visits per 100, whereas for males the rate was 2.8 per 100 persons. Visit rates increased by age in both sexes, but no significant difference was observed for age-specific rates by sex in any age group. Nearly 88% of all visits were made by white patients. The average visit rate for white individuals was 3.7 visits per 100 persons, whereas it was 3.0 visits per 100 black persons. The findings from the NAMCS in 1992 showed that black patients accounted for about 36% of the glaucoma-related visits to the hospital outpatient departments compared to approximately 61% by the white patients. There were some geographical differences in the office visit rates. In the South the visit rate was 4.3 visits per 100 persons compared to 2.1 visits per 100 persons in the West.

General ophthalmologists saw about 76% of glaucoma patients, and the rest were taken care of by glaucoma specialists. Although 68.1% of all new patients were referred by other physicians, only 6.8% of glaucoma patients had such a referral. Even the referral rate for patients with diagnoses other than glaucoma was better—31.6%. Patients making return visits composed 90%, of the total, whereas 10% of visits were by new patients. Approximately 17% of all visits made by subjects in age group of 45 to 64 years were for new problems compared to 9% of those 65 years of age and older. The mean physician–patient contact time during glaucoma visits was 21.7 minutes compared to 17.3 minutes for other office visits.

What Are the Sources of Payments for Office Visits?

For the period 1991–92, payment sources for patient visits were Medicare (61.9%), private insurance (36.6%), self-payment (18.8%), Medicaid (8.0%), Health Maintenance Organization/prepaid (7.1%), other government (4.7%), other (2.9%), no charge (1.2%), and unknown (0.8%).

What Are the Reasons for Patient Visits?

The NAMCS provides detailed information on the reasons for office visits by glaucoma patients during 1991–92. The various reasons, in descending order of frequency, were diagnosis of glaucoma (46.9%), diagnostic screening and preventive measures (27.2%), treatment (9.7%), symptoms (9.4%), other (5.8%), and test results (1.0%). Among patients returning for diagnostic tests, about one-third had one diagnostic test, and approximately half had two diagnostic tests.

Are There Any Resource Centers for Glaucoma Information?

There are several national and international organizations concerned with the problems associated with glaucoma. Table 2–6 lists Internet Web sites providing a wide range of information concerning glaucoma.

Are There Public Awareness Programs for Glaucoma?

The largest public-awareness program is the glaucoma portion of National Eye Health Education Program (NEHEP), funded by the National Eye Institute in 1991. The National Society to Prevent Blindness (NSPB) has a very active ongoing program schedule such as Glaucoma High-Risk Alert, National Glaucoma Awareness Week, an Eye-Saving Sabbath, a National Center for Sight information clearinghouse, Fight For Sight research awards, an industry safety program, a patient brochure series, implementation of a screening pilot study, and formation of a coalition of African-American organizations. The chief aim of all the programs is to make the public fully aware of the importance of periodic ophthalmologic examinations especially among high-risk groups.

What Type of Counseling Is Required in POAG?

As eyesight is so essential for social and economical health, many glaucoma patients fall into depression, often feeling desperate and helpless. The treating physician should be aware of the signs and symptoms of depression and be willing to provide information and support. The family members can be a great source of information regarding the extent of the problem. Drug-related psychiatric side effects might be resolved by altering medications. The most common offenders are CAIs and beta-blockers. Employers may need letters from the physician explaining the extent of visual disability and other handicaps. For example, the patient may not be able to return to jobs requiring the use of heavy machinery or night shifts. Some patients may benefit from currently available low visual aids. Others may require referrals to glaucoma resource centers, social agencies, and psychiatrists.

Table 2–6. Web Sites Pertaining to Information Regarding Glaucoma

Name of Organization	Web Address	Description
American Academy of Ophthalmology	www.eye.net	Site sponsored by the American Academy of Ophthalmology that provides information on all issues of ophthalmology including glaucoma
Glaucoma Foundation, New York	www.glaucoma-foundation.org	Patient-oriented site that also has an on-line newsletter, *Eye to Eye*.
Glaucoma Research Foundation, San Francisco	www.glaucoma.org	Provides information on glaucoma research and includes access to the Glaucoma Support Network, which matches patients with a network volunteer.
Web-Xpress	www.web-xpress.com	A public Web site development company founded by ophthalmologists. By clicking on Clients, users can access the International Society of On-Line Ophthalmologists, Glaucoma Association of New York, the Ohio Society of Ophthalmology, and many others
International Society of On-Line Ophthalmologists	www.web-xpress.com/isoo/glaucoma	The site for clinicians includes cyber panels, global grand rounds, continuing medical education, and a forum for subspecialties including glaucoma.
Glaucoma Associates of New York	www.web-xpress.com	Information is available to both patients and health care professionals.
Internet Patient Support Group	Alt.support.glaucoma	This site is an on-line patient support group supported by Glaucoma Associates of New York.
Glaucoma Eye-Mail	majordomo@lists.ascrs.org	This site is sponsored by the American Society of Cataract and Refractive Surgery. It lets members instantly exchange glaucoma information from around the world via e-mail.
Glaucoma Network	www.glaucoma.net	Provides access to the Web sites of Glaucoma Associates of New York and the New York Glaucoma Research Institute.

What Is the Effect of Glaucoma on the Patient's Quality of Life?

Visual loss including other social and economical factors may adversely affect a patient's quality of life. Sherwood and coworkers[146] compared the quality of life between patients with glaucoma and a control group. In the former group there was a statistically significant difference in physical functioning, role functioning, social functioning, mental health, and health perceptions. Similarly, they showed statistically significant differences in day vision, night vision, far vision, near vision, glare impact, and overall vision. Patients with glaucoma also complained significantly more of day sleepiness, lack of energy, and eye aches. Increasing glaucoma damage was associated with decreasing quality of life perception. Mobility performance was found to be decreased in individuals with glaucoma as compared to persons with normal vision.[147] For instance, the former walked, on the average, 10% slower than the latter. Herbert and associates[148] found that compared to white Americans, black Americans tend to rely more on family, immediate community, and religion to cope with the effects of disease on their lives.

Future Considerations

Where Is Glaucoma Research Heading?

There is an acute need for ways to diagnose glaucoma early and to provide neuroprotection to healthy as well as injured ganglion cells. Genetic testing for defective genes opens a new avenue toward early diagnosis and possible therapy. Borrás and associates[149] have demonstrated transfer of genes to the trabecular meshwork and expression of recombinant proteins in rabbits after injection of replication-deficient adenovirus vectors into the anterior chamber. Similarly, Kaufman and coworkers[150] used a herpes viral vector (ribonucleotide reductase defective HSV-1, hrR31) to deliver the lacZ reporter gene to living cat and rat eyes.

A device that can measure IOP continuously without the patient having to visit a physician would also answer the difficult question of diurnal variation. Accordingly, medical therapy might be altered to address IOP fluctuations during the course of the day.

The field of neuroprotection has opened exciting possibilities. Current research is focusing on determining relevant mechanisms involved in retinal ganglion cell degeneration by studying cellular changes in the optic nerve and retina. The ultimate aim is to prevent retinal ganglion cell loss. Neufeld and associates[151] have demonstrated inducible nitric oxide synthase (NOS-2) in the optic nerve heads from human glaucomatous eyes and from rat eyes with chronic, moderately elevated pressure. They treated rats with unilateral elevated pressure with aminoguanidine, an inhibitor of NOS-2 for 6 months and compared that to an untreated group. At the end of the study the untreated group showed pallor and cupping, whereas the treated group appeared normal. When they calculated retinal ganglion cell loss by labeling with Fluoro-Gold, the cell loss in the treated group was 10% compared to 36% in the other group. The investigators believe that excessive nitric oxide released by reactive astrocytes stimulates the production of peroxynitrite, which is toxic to the axons of retinal ganglion cells at the level of lamina cribrosa. This epic finding

opens new doors for designing neuroprotective agents in the near future. Drugs that block excitotoxic ganglion cell loss or those that bar NOS, such as arginine analogues, may have a role in the treatment of glaucoma. Memantine, which blocks excessive or pathologic NMDA receptor-linked ion channel activity but relatively spares normal or physiologic activity, is being tried in clinical glaucoma trials in the United States as a potential neuroprotective agent.[152,153] It is already used for the treatment of dementia and Parkinson's disease.

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◆ 3 ◆

Glaucoma Suspects

Kimberly S. Warren and Manijeh Contractor

Definition

How Are Glaucoma Suspects Defined?

Glaucoma suspects (or ocular hypertensives) may be defined as individuals with intraocular pressure (IOP) repeatedly above 21 mm Hg and/or appearance of the optic disc and/or nerve fiber layer that is indicative of glaucomatous optic nerve damage, but with normal visual fields. Appearance of the optic nerve head, which may lead to a suspicion for glaucoma, includes a large cup-disc ratio, narrowed disc rim, asymmetry of disc cupping between the two eyes, optic disc notching or hemorrhage, and peripapillary atrophy. These findings may be seen in conjunction with normal visual fields, adult onset, and normal gonioscopic examination. Known secondary causes of increased IOP or nerve damage, such as pigment dispersion, ocular trauma, and pseudoexfoliation, are excluded from the definition.

What Additional Factors Are Considered in the Definition of Ocular Hypertension?

There are some known risk factors that may make a patient "high risk" for developing glaucoma. These risk factors include advanced age, positive family history of glaucoma, myopia, black race, elevated IOP, and systemic diseases such as diabetes, cardiovascular disease, and hypertension.[1–3] As the number of risk factors increases, the likelihood that an individual may develop glaucoma over a certain period of time also increases. Patients who are considered glaucoma suspects and demonstrate multiple risk factors must be carefully watched.

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How Important Is IOP in Glaucoma Suspects?

The majority of patients with elevated IOPs do not develop glaucoma during their lifetimes. The higher the initial IOP, the more likely the individual may develop visual field loss. Armaly[4] found that 6 to 12% of eyes with IOP in the range of 20 to 30 mm Hg on initial examination would develop visual field loss. This increased to 30% when the IOP was more than 30 mm Hg. Older patients also have a greater incidence of visual field loss.

There is still a lot of controversy regarding the use of term *glaucoma suspect*. Some ophthalmologists have strongly preferred the terms *ocular hypertension*, and *incipient glaucoma*. Approximately 5% of the general population have IOPs higher than 22 mm Hg and are known as ocular hypertensives. Although Armaly[1] found in a 10-year follow-up study that 1.1% of ocular hypertensives individuals developed glaucoma, Lundburg et al[5] found in a 20-year follow-up study that 34% of their subjects develop glaucoma. There is a definite and strong association between elevated IOP and glaucoma. Approximately 30% of the glaucoma patients have IOPs greater than 22 mm Hg.[6–9] Therefore, patients with ocular hypertension are theoretically a heterogeneous group composed of preglaucoma and healthy subjects with IOP in the upper 5% of the normal range.

Epidemiology and Importance

Why Is Understanding of IOP Important in Studying Glaucoma Suspects?

As IOP is intimately related to glaucoma, it is essential to know its distribution and the factors that affect it. One of the first major population studies regarding the distribution of the IOP was undertaken by Leydhecker and Krieglstein[10] in Germany. They measured IOP using Schiøtz tonometry on approximately 20,000 individuals, none of whom was known to have glaucoma at the time of examination. The authors found that the distribution of IOP in this population resembled a bell-shaped curve, but with skewing toward the higher levels. They calculated that the population's average IOP was approximately 16 mm Hg, with a standard deviation of about 2.5 mm Hg.

IOPs over 21 mm Hg fell beyond two standard deviations from the mean, and therefore was considered abnormal. One should recognize that this abnormal level was reached solely by statistical methods. Eyes are different in their susceptibility to the effects of pressure. Some individuals develop glaucomatous damage at IOPs near the population mean, whereas others maintain normal optic nerve and visual functions for many years despite IOPs of 30 or even 40 mm Hg. Glaucoma is diagnosed only when there is detectable damage to the optic disc and/or visual fields.

Most studies have found that average IOP increases with age.[11] Measurements of IOP at different times of the day often yield different readings, being higher in the morning than in the afternoon or later in the day. Pressures in some individuals may be somewhat higher in the winter than in the summer.[12,13] There is also evidence that the IOP is slightly higher in women than in men after the age of 40.[14] Patients with a family history of glaucoma,[11,14] of

African-American descent,[1] and those with diabetes show a strong tendency toward higher mean pressures than the general population.

How Common Are Glaucoma Suspects Compared to Patients with Primary Open-Angle Glaucoma?

It is estimated that 2.25 million people in the United States over the age of 40 years have primary open-angle glaucoma (POAG),[14] and approximately half are unaware of their disease despite demonstrable visual field loss.[2] Another 10 million Americans are believed to have IOPs greater than 21 mm Hg; approximately 10% of these eyes may convert to POAG over the course of a decade.[3]

The concept of ocular hypertension is very important because although most glaucoma patients have elevated IOP, not all subjects with elevated IOP have glaucoma. Moreover, a majority of people with ocular hypertension may not develop glaucoma during their lifetimes. Ocular hypertension is present in up to 18% of people over 40 years of age of African-American descent compared with 13.6% of mixed race and only 4.6% of whites in the same age group.[15]

Who Is at Risk for Being a Glaucoma Suspect?

For many years, ophthalmologists have placed varying degrees of importance on the role of IOP in glaucoma. There is good evidence that IOP is a major risk factor for glaucomatous optic nerve head damage.[16] Elevated IOP is present in a majority of glaucoma cases at initial screening.[17,18] Population-based studies indicate only one-tenth or less of those with elevated IOP have glaucomatous visual field loss.[18] Also, IOP varies in both glaucomatous and normal individuals over time. The proportion of glaucomatous subjects with elevated IOPs increases with time: 50% at screening, 75% at screening plus one follow-up, and 85% with screening and multiple follow-up checks.[18] The hypothesis that elevated IOP is a major factor in chronic glaucomatous optic atrophy and that control of IOP usually has a favorable influence on its progression is widely accepted. One study noted that none of the study patients with IOP equal to or less than 16 mm Hg progressed, whereas all of the patients with pressure equal to or greater than 22 mm Hg worsened over a 4 to 11-year follow-up.[19] Of patients with an IOP between 17 and 21 mm Hg, 50% progressed. Another study found that the number of subjects experiencing visual loss annually was twice as great when mean IOP was greater than 18 mm Hg, compared to IOP less than 18 mm Hg.[20] The rate was four times greater when IOP measured more than 22 mm Hg. David and associates[8] highlighted various differences between black and white individuals with ocular hypertension. They showed that 65.9% of black patients presented with IOPs higher than 26 mm Hg as compared to 26% of white patients. In both groups, the risk of glaucoma was directly related to the initial IOP. Black patients with ocular hypertension have a higher risk of developing glaucoma than white patients. Black patients with ocular hypertension were also 12.6 years younger than their white counterparts.

Higher rates for glaucoma have also been reported among some Caribbean populations. In the Barbados Eye Study (BES), a high prevalence of POAG was detected with increasing age.[21] One in 11 persons older than 50 years had

POAG. This estimate increased to one in nine at ages over 60 years and to one in six in those over 70 years. Although IOP may contribute to the high prevalence of POAG, genetic-environmental interactions also play an important role in its pathogenesis. This study also highlights the differences between ocular hypertension and POAG.[22] Ocular hypertension in the black population of the BES was linked to the high prevalence of systemic hypertension and diabetes. Patients with large body sizes, measured by body mass index, demonstrated higher IOPs. Although obesity is related to hypertension and diabetes, the association between larger body size and IOP was found independently of these two variables. An association between obesity and IOP was also found in the Japanese population.[23,24] Increased pigmentation was correlated with an elevated IOP in the BES. Gender association with open-angle glaucoma has also been shown in the Framingham Study.[25] Men were more than twice as likely as women to have open angle glaucoma (2.5 % vs. 1.4 %). However, the results of a Swedish study were the opposite.[26]

A Greek study evaluated risk factors for conversion from ocular hypertension to POAG in 345 untreated glaucoma suspects.[27] Twenty percent of the patients developed confirmed glaucoma. Family history, age greater than or equal to 60 years, axial myopia, and arterial hypertension were reported to be significant risk factors for visual field loss.

Are There Any Geographical Differences in the Distribution of Glaucoma Suspects?

Glaucoma is the second leading cause of blindness worldwide.[9,28] In the year 2000, it is estimated that there may be approximately 66.8 million people globally with glaucoma and 6.7 million of these individuals may have bilateral blindness.[28] As a result, glaucoma has been the subject of many population-based studies among major ethnic groups in the world.[28–30]

In the United States, POAG has been reported to affect between 1.5 and 2.1% of the population.[6,18,25,31] Ocular hypertension occurs in 4 to 10% of the population over the age of 40.[31] It is important to evaluate the ocular hypertensive group, as it is estimated that 10% of these individuals may eventually develop POAG.[32]

Mitchell and coworkers[33] investigated the prevalence of open-angle glaucoma and ocular hypertension in an older Australian population. Open-angle glaucoma had a prevalence of 3.0%, whereas ocular hypertension was present in 3.7% of patients. The highest prevalence of 4.1% was found in the age group of 60 to 69 years and in individuals older than 80 years. The prevalence of glaucoma was higher in women after adjusting for age. But there was no sex difference in the age-adjusted prevalence of ocular hypertension.

Nearly half of the world's estimated 5.1 million people who are blind because of glaucoma reside in East Asia.[29] In an urban, South Indian population, prevalence of POAG was 4.1% and ocular hypertension was 30.8%.[34] Interestingly, angle-closure glaucoma was reported to be 43.2% higher than both POAG and ocular hypertension combined.

A population-based, collaborative glaucoma survey was conducted in seven regions throughout Japan, during the years of 1988 and 1989. The findings at

the time of screening included angle-closure glaucoma (34%), POAG (0.58%), low tension glaucoma (2.04%), and ocular hypertension (1.37%). The very high prevalence of low tension glaucoma and extremely low prevalence of ocular hypertension in the Japanese might reflect a racial peculiarity and the age-specific trend of the reduced IOP with advancing age. The prevalence of primary angle-closure glaucoma was found to be much higher in Japanese than in Caucasians, with a predilection for women. The Japanese also showed a progressive decrease in myopia with age.[35]

Diagnosis and Differential Diagnosis

How Is the Glaucoma Suspect Identified?

A careful history and examination are important in the diagnosis of ocular hypertension or glaucoma suspect (Fig. 3–1). A thorough history should be obtained. There are generally no reported symptoms, and an elevated IOP or a suspicious disc is found on routine eye examination. The patient's age, race, and family history of glaucoma should be identified. The practitioner must inquire about past medical and ocular problems including congenital abnormalities, myopia, and systemic vascular diseases.

What Conditions Can Mimic Glaucomatous Nerves?

There are some individuals born with anomalous optic discs, which may mimic glaucoma type changes. These include a physiologically large cup-disc ratio, optic nerve asymmetry, and peripapillary atrophy. Patients with myopia often have tilted anomalous discs that can appear to have nerve loss. Systemic vascular diseases such as hypertension, cardiovascular disease, and atherosclerosis can also lead to loss of the nerve fiber layer and cause disc hemorrhage that can signify glaucomatous changes.[36]

What Findings in the Exam Lead to the Diagnosis of Glaucoma Suspect?

During ocular examination an IOP above 21 mm Hg, abnormal or suspicious optic disc findings, and multiple risk factors should make a clinician suspect glaucoma. As defined earlier in this chapter, suspicious optic nerve appearance includes an increased cup-to-disc ratio, asymmetry of the cups, notching, disc hemorrhage, and peripapillary atrophy. The diagnosis of a glaucoma suspect is made if gonioscopy and visual field analysis are within normal limits.

Are There Better Ways of Detecting Glaucoma Other Than Visual Fields and Optic Nerve Changes?

Nerve fiber layer defects have been shown to precede visual field defects in patients who progressed from a glaucoma suspect to POAG. In some studies the nerve fiber demonstrated changes 5 years before visual field changes.[37,38]

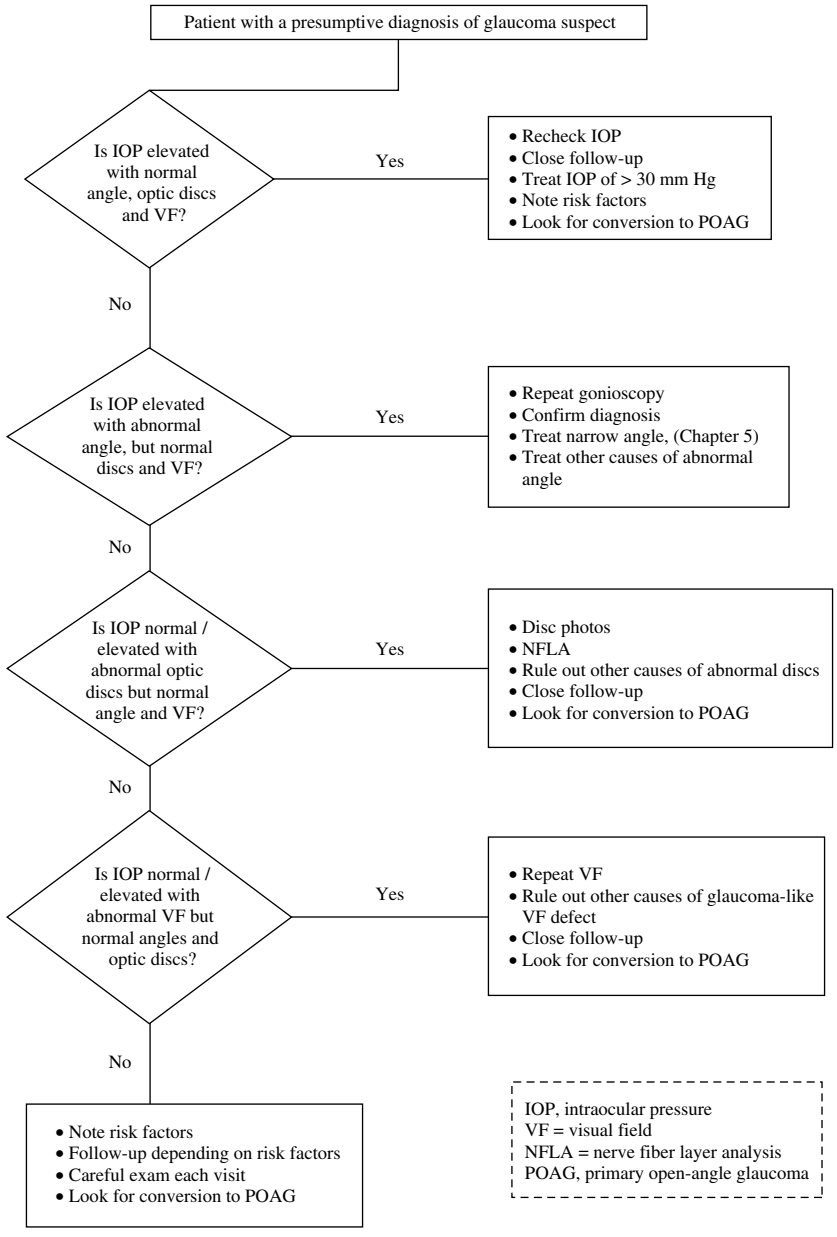

Figure 3–1. Algorithm for management of glaucoma suspects.

Studies by Quigley report that 40% of optic nerve fibers may be lost before there is a change noted on visual field testing.[39] There have also been reports that scanning laser polarimetry shows a reduction in the nerve fiber layer levels when ocular hypertensive patients are compared with normals.[40]

How Is Elevated IOP Related to Optic Nerve Damage?

Several hypotheses have been proposed in this regard. The first hypothesis (vascular theory) suggests that POAG represents a progressive anterior ischemic neuropathy, which is usually a result of elevated IOP. It is important to realize that perfusion of the optic nerve head is dependent on blood pressure at the level of the optic nerve, the capillary circulation in the optic nerve head, and the IOP itself. This explains why subjects differ in regard to the resistance of their optic nerve to increased IOP and why some individuals with microvascular diseases such as diabetes are more likely to develop glaucoma.

The second hypothesis, mechanical theory, suggests that POAG is due to a progressive optic neuropathy caused by the mechanical effect of IOP on the lamina cribrosa. Elevated IOP produces distortion and partial collapse of the lamina's supportive structures, causing compression of the optic nerve fibers as they pass through. This will lead to the blockage of the axoplasmic flow and eventually destruction of the nerve fibers. Visual field loss would depend on the resistance of the lamina cribrosa to compression from the elevated IOP.

Experimental studies have shown that the holes and pores in the lamina cribrosa tend to be larger at the superior and inferior poles of the optic disc. Accordingly, the supporting structure of the lamina is less rigid in these areas and more likely to collapse when the IOP is elevated. This explains why progressive disc cupping usually precedes the development of visual field defects. Similarly, it may explain why young patients with less rigid laminar supporting tissue show rapid changes in the cupping when IOP is elevated, and why they show reversibility of cupping when IOP is normalized. Clinically, the initial damage is also seen at the upper or lower poles of the disc.

Is There Evidence of Abnormality in Blood Flow in Glaucoma Suspects?

In several studies, the abnormalities of the blood flow in POAG has been shown using color Doppler imaging,[41,42] fluorescein angiography,[43] laser Doppler flowmetry,[44] and pulsatile ocular blood flow measurements.[45]

Other investigators have shown evidence of reduced blood flow at the level of the lamina cribrosa and temporal neuroretinal rim. Kerr and associates[46] used scanning laser Doppler flowmetry images of the optic disc. Pulsatile ocular blood flow readings were performed on patients in the sitting, standing, and supine positions. The authors found significant reduction in the blood velocity, volume, and flow at the lamina cribrosa and temporal neuroretinal rim in glaucoma patients compared to patients with ocular hypertension. They found no difference between the groups when evaluating the nasal neuroretinal rim or nasal juxtapapillary retina. The ocular pulse amplitude, pulse volume, and pulsatile ocular blood flow were significantly lower in glaucoma compared to ocular hypertensives in the sitting and standing positions.

In 1973, Drance et al[47] reported a "hypercoagulable state" theory in patients with normal pressure glaucoma. They showed that these patients had a greater tendency to develop thrombosis. Several other studies have also shown that patients with POAG, when compared with normal pressure glaucoma and a

control group, had an elevated level of clotting cascade and fibrinolysis pathway (prothrombin fragments 1 + 2 and D-dimer).[48]

These findings give evidence of disturbance in ocular circulation in POAG. It is not clear if this is the primary cause of the disease or one of the complex collection of secondary changes that occur in glaucoma.

There are some published data relating to ocular blood flow in ocular hypertension. Some studies have shown no significant difference between normal and ocular hypertension, whereas others found evidence of impaired circulation in ocular hypertensives using fluorescein angiography.[49] The response of ocular blood flow to artificially elevated IOP in the acute situation has been studied in animal models.[50] In normal human volunteers, blood flow circulation in the retina, choroid, and optic disc were studied with the use of suction cups to elevate IOP.[51] The velocity of the blood flow, as measured with fluorescein angiography, was reduced at increased levels of IOP. The reduction in choroidal circulation was more marked than that in the retina. Differences in anatomic and physiologic characteristics of choroidal and retinal blood vessels appeared to account for this observation. IOP and age may alter the ocular blood flow in the absence of disease.[52]

Treatment and Management

How Often Should the Glaucoma Suspect Be Followed?

An ocular hypertensive or glaucoma suspect requires follow-up at regularly scheduled visits. The exams should include visual acuity, tonometry, optic nerve analysis, and periodic visual field testing. Baseline stereoscopic optic disc photos are helpful when analyzing the nerve for progressive changes characteristic of glaucoma. There has been recent advancement in the field of digital imaging that may be able to detect visual field loss prior to the conventional visual field testing. This method of nerve fiber layer analysis may help us detect patients who are destined to develop POAG at an earlier date and begin treatment.

When Should Medical Treatments Be Started in a Patient with Ocular Hypertension?

Therapy should be started if there is evidence of optic nerve or visual field changes consistent with early POAG. Some physicians may also treat based on a certain level of IOP regardless of normal appearing discs and visual fields. The level of ocular hypertension and the prevalence of optic nerve or visual field damage has been studied and correlated. A study by Strumberg[53] showed that 29% of eyes with an IOP from 30 to 36 mm Hg showed some degree of measurable damage and 72% of eyes with IOP greater than 36 mm Hg showed damage. Stamper et al[36] also found similar correlations with 28% of eyes with an IOP greater than 30 mm Hg showing damage. Pohjanpelto and Palva[54] reported that 11% of eyes with IOP from 30 to 34 mm Hg and 27% of eyes with IOP 35 to 39 mm Hg showed changes consistent with POAG. Based on these studies, most physicians would treat ocular hypertension when the IOP reaches 30 mm Hg or greater consistently.

Do Other Factors Besides IOP Initiate Early Medical Treatment?

In addition to those with significantly elevated IOP (i.e., >30 mm Hg), patients with multiple risk factors should be considered for early treatment. For example, an African-American patient with a positive family history of glaucoma, who is also being treated for systemic hypertension, would be considered for early treatment even if the visual field tests were normal. Monocular patients should be watched very carefully, and initiating early treatment may be appropriate. A patient with unreliable visual fields or difficult follow-up exams should be considered for treatment as well. Patients who are anxious and very concerned about the possibility of progression to POAG should be counseled by the physician. Treatment and follow-up may be based on the physician and patient comfort levels. A patient with a previous vascular event in the fellow eye may also be considered for early therapy.

What Initial Medical Therapy Should Be Started?

In the treatment of ocular hypertension, it is best to begin with a monocular trial to ensure the efficacy of the drug. First-line therapy should be initiated after a thorough medical and ocular history to determine any contraindications to certain drugs. Depending on the patient, first-line therapy includes topical β-adrenergic antagonists, prostaglandin analogues, α-agonists, and topical carbonic anhydrase inhibitors. Systemic carbonic anhydrase inhibitors, miotics, argon laser trabeculoplasty, filtering, and tube-shunt procedures are routinely not indicated for the ocular hypertensive patient.

Do All Glaucoma Suspects Develop Glaucoma?

The majority of the individuals with ocular pressure greater than 21 mmHg did not develop visual field change with a follow-up of at least 5 years.[55] Linner[56] studied 10-year follow-ups of ocular hypertensive patients, and found that the mean value of pressure in those subjects examined at the beginning of the study and at 5- and 10-year intervals showed a statistically significant decrease. The identification of susceptible ocular hypertensive patients who may develop glaucoma is an unsolved clinical problem.

Future Considerations

What Are Some of the New Techniques Used to Analyze the Optic Nerve Head and the Nerve Fiber Layer?

There has been recent advancement in the technology used to analyze the optic nerve head and the nerve fiber layer. Some of these advancements include scanning laser tomography, scanning laser polarimetry, and optical coherence tomography (OCT). The Heidelberg retina tomograph (HRT) uses a diode laser that is projected onto the retina using a confocal system. The depth of the scanning rage is 0.5 to 4.0 mm. The instrument performs 32 consecutive scans and

covers a rectangle of 10 x 10 degrees. According to a report by the American Academy of Ophthalmology (AAO),[57] there are advantages and disadvantages of each of the above methods. The advantages of the HRT are that (1) images can be obtained in an undilated pupil, (2) it uses low light intensity, and (3) a real-time image can be obtained for immediate evaluation. Disadvantages of the HRT are the cost and that it requires a reference plane. The HRT targets both the optic nerve head and the nerve fiber layer for analysis.

The scanning laser polarimeter measures the nerve fiber layer by using a confocal scanning laser ophthalmoscope with an integrated polarimeter. The GDx Nerve Fiber Analyzer is an example of this technology. Scanning laser polarimetry measures the thickness of the retinal nerve fiber layer. The advantages outlined by the AAO[57] include (1) quicker and more objective polarimetric reading than visual fields; (2) a greater sensitivity than the glaucoma hemifield test; (3) measurements are obtained without a reference plane and independent of magnification; and (4) it is independent of the optical resolution of the human eye. Some of the disadvantages are (1) other polarizing structures of the eye might interfere with retardation, and (2) peripapillary atrophy and chorioretinal scarring may also increase retardation. Scanning laser polarimetry targets analysis of the nerve fiber layer.

OCT is a high-resolution technique that is an optical analogue of ultrasound B-scan. It uses an 850-nm diode laser to obtain cross-sectional images of the posterior segment. The advantages of OCT include: (1) no reference plane is required, and (2) it is not affected by the refractive state of the eye. Disadvantages include: (1) cortical and posterior subcapsular cataracts may impair performance, and (2) it requires pupillary dilation. The target of this instrument in glaucoma evaluation is the nerve fiber layer. It also can be useful in diagnosing macular disorders and other retinal pathologies.

Can These New Techniques Differentiate Glaucomatous from Nonglaucomatous Eyes?

The techniques are relatively new; however, there has been some evidence to support their ability to detect glaucomatous changes. Mistlberger et al[58] found that both HRT and OCT could differentiate glaucomatous from nonglaucomatous eyes. In the same study, however, the OCT showed no difference between normal and ocular hypertensive eyes. There have been other studies that claim HRT is able to demonstrate optic disc change before the development of field defects in a group of ocular hypertensives converting to early glaucoma.[59] More studies and evaluations are needed to determine how best to use this new technology in the treatment of ocular hypertension.

Is There a Role for Neuroprotective Agents in Patients with Ocular Hypertension?

This is an interesting concept in the ocular hypertensive patient. Should patients be started on a neuroprotective agent to prevent the progression to POAG? If so, which patients should be started on neuroprotective agents and how should they be followed? Is nerve fiber layer analysis the best way to fol-

low this category of patients? These are very important questions and more research needs to be done to see if certain medications can be used in the ocular hypertensive patients to protect them from future damage.

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Normal Tension Glaucoma

Thomas K. Mundorf

Definition

What Is Normal Tension Glaucoma?

Normal tension glaucoma (NTG) is a progressive optic neuropathy that mimics primary open-angle glaucoma (POAG) but lacks the findings of elevated intraocular pressure (IOP) or other mitigating factors that can lead to optic neuropathy. It includes the findings of normal angles on gonioscopy, cupping of the optic nerve, and visual field loss correlating with the cupping and may show progressive damage of the nerve. It is believed to have other influencing factors such as vascular and genetic.

Epidemiology and Importance

How Common Is NTG?

Klein et al[1] found the incidence of NTG in the Beaver Dam Eye Study to approach 33%. In Asian populations, such as in Japan, as the patient's age increases, there is a decrease in average IOP, resulting in a higher percentage of glaucoma patients falling into the normal tension group.[2] In fact, as much as two-thirds of the glaucoma in Japan may fall into the category of NTG.[3]

What Are the Demographic Characteristics of NTG?

Different studies show varying results in evaluating the occurrence of NTG among men and women. Levene[3] found in his review that there were more women with NTG, but the Beaver Dam Eye Study[1] showed no predilection for either sex. With women having a longer life span, it may be understandable to see more females with NTG (along with other chronic disorders).

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Are There Any Genetic Characteristics of NTG?

With regard to inheritance, Werner[4] found cases of POAG and NTG within the same family. Miglior[5] and Geijssen[6] also showed a predilection for several members of the family having NTG. It would be judicious to suggest that other family members not already evaluated be examined by an ophthalmologist.

What Role Does IOP Play in NTG?

Although IOP is generally normal (10–21 mm Hg), several studies include 22 to 24 mm Hg in NTG. The collaborative normal tension study had 24 mm Hg as the upper limit.[7] Kamal and Hitchings[8] cite a mean IOP of less than or equal to 21 mm Hg, with no more than a single reading of up to 24 mm Hg as still indicative of NTG.

Crichton et al[9] found that a 2 mm Hg or greater difference in IOP correlated with greater visual field loss in the eye with the higher pressure; 13 of 47 patients with NTG in this study had asymmetric IOP of ≥1 mm Hg. However, many patients with asymmetric visual field loss showed symmetric IOP. Crichton et al allowed an IOP of ≤23 mm Hg to define NTG in this study.

Araie et al[10] found a correlation between IOP and visual field progression in this study of 56 eyes. However, Levene's[3] review in 1980 did not find convincing evidence that IOP played a role in NTG. Another study discussed under the treatment of NTG show that lowering IOP helps to slow if not halt progression.[7]

What Role Might Blood Flow Play in NTG?

Aside from IOP, blood flow in the NTG patient has held a fascination for many researchers. The idea that abnormal blood flow, intermittent or persistent, leads to decreased profusion of the optic nerve, which results in ischemia and decreased nutrition, has been postulated as a significant etiologic factor in the pathogenesis of NTG. Increases in the incidence of migraine and vasospasm in patients with NTG has been investigated by Phelps and Corbett.[11] Drance and his colleagues[12] showed that capillary flow in the fingers of NTG patients was decreased, and this evidence offered vasospasm as a possible causative factor in NTG. Others have found increased vascular resistance by carotid Doppler imaging (CDI) in patients with NTG.[13] Netland et al[14] and Kitazawa et al[15] found some patients with NTG had less progression if they were on systemic calcium channel blockers. This finding led both groups to suggest that vasoregulation in NTG might be abnormal. Flammer[16] felt that calcium channel blockers had a role in controlling vasospasm (seen in narrow bed capillary blood flow) and potentially stabilizing the disease process.

It has been shown that NTG patients, more so than other patients, may be more susceptible to vasodilators such as carbon dioxide.[17] Pullinat et al[17] went on to suggest that this was due to an already-present predisposition to vasoconstriction in patients with NTG.

Hayreh et al[18] suggested in 1994 that episodes of nocturnal hypotension might explain the progressive optic nerve damage and visual field loss in patients with NTG despite normal IOP. They found that these patients had a deeper drop in nighttime blood pressure than in patients with POAG. They

went on to postulate that these patients might be more prone to progression if their blood pressure was aggressively treated. Graham and associates[19] found more progression in NTG and POAG patients if they had a lower nocturnal blood pressure.

Meyer et al[20] compared 20 NTG patients with 20 normal patients. Blood pressure was monitored over 24 hours at 20-minute intervals during the day and 40-minute intervals during the night. They found a significant blood pressure drop in many patients, which was more pronounced in the normal tension patients versus the controls. This drop was thought to have a role in the pathogenesis of NTG.

Fontana et al[21] investigated pulsatile ocular blood flow (POBF) in normal and NTG patients. They found that the POBF was lower in the normal tension group. They also found that if there was asymmetry between the two eyes of an NTG patient, there was a higher incidence of unilateral visual field loss in the eye with the lower blood flow. James and Smith[22] evaluated 29 normal patients and 22 NTG patients and also found lower POBF in the normal tension group. Peripapillary retinal blood flow in NTG was investigated by Chung and associates,[23] who found that the normal tension group compared to controls had a larger area of reduced blood flow in the peripapillary area. They felt that this could contribute to retinal ganglion cell death and progression of disease.

What Other Findings May Be Present in Patients with NTG?

Carter and associates[24] looked at laboratory findings in patients with high tension glaucoma, NTG, and controls. No significant difference was seen between the three groups with regard to coagulation factors, cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, and hemoglobin A_{1C}. Plasma viscosity was also shown to be similar in these three groups.

Wax et al[25] have investigated the presence of autoimmune antibodies and their potential relationship to glaucoma, especially NTG. Antibodies to retinal proteins were found in higher concentrations in patients with NTG compared to controls. Deposition of these compounds were found in the layer of retinal ganglion cells and in the inner nuclear and outer nuclear layers. The authors hypothesized that these antibodies could have a role in apoptosis. Romano et al[26] published a study showing that the concentration of anti-rhodopsin antibodies in serum was elevated in patients with NTG. It has been shown that stress can cause an increase in heat shock proteins, which are neuroprotective by design, but are also antigenic. The resultant antibodies to these heat shock proteins may have the potential to allow damage to occur.[27] Wax et al[25] found 12% of the NTG patients in the study exhibited an increased level of monoclonal gammopathies, leading them to suggest a similarity to patients with progressive peripheral neuropathies associated with monoclonal paraproteinemia.

Cartwright and Anderson[28] reported a 30% prevalence of autoimmune disorders by epidemiologic criteria in patients with NTG. The prevalence of immune-related disorders may have been a factor in the vascular system, making vasospasm or constriction potentially more serious in this group of patients.

Diagnosis and Differential Diagnosis

What Are the Findings in NTG?

Cupping of the optic nerve is often the first finding to suggest NTG. Optic nerve cupping is generally similar to that seen in open-angle glaucoma. The existence of cupping specific to NTG is debated. Some investigators feel that cupping in NTG has more severe slopes,[29] with visual field loss exceeding the degree of cupping, but no definitive study has substantiated this theory.[3]

The amount of peripapillary atrophy may also influence vision according to the work done by Park and associates.[30] Tezel et al[31] compared patients with NTG, ocular hypertension, and POAG, looking for disc changes characteristic for each group. Noting more nerve loss, this research has suggested that the NTG patients may have presented later in their course. Miller and Quigley[32] found no difference between NTG patients, POAG patients, and controls. These physicians found what they felt was a difference in the lamina cribrosa's structure that possibly could be a factor in the etiology of NTG. Geijssen and Greve[33] divided NTG into three groups: myopic, focal ischemic, and senile sclerosis. Their work suggested that the prognosis varied with each group.

Disc hemorrhages have also been linked to NTG; however, several studies have lessened this tie.[31,34] Although it is generally agreed that a disc hemorrhage is evidence of future nerve fiber drop out, it is not specific for patients with NTG.[35] Seigner and Netland[36] described the prognostic value of optic disc hemorrhage in glaucoma, where a disc hemorrhage is interpreted as an indicator of uncontrolled glaucoma.

Topography of the optic nerve in patients with NTG has been investigated for characteristics possibly specific to this entity. Compared to the findings in 50 NTG patients and patients with POAG, disc parameters gathered with the scanning laser tomographic technology (Heidelberg retinal tomography, HRT) showed no significant difference between the groups.[37] Although disc differences between patients with glaucoma were different from the controls and from the patients with ocular hypertension, no distinction was found between the groups with pathology (POAG and NTG).

Stroman et al[38] looked at optic nerve characteristics from magnetic resonance imaging (MRI) studies; 20 controls and 20 patients with NTG showed no statistical difference between the groups. There was a significant increase in the incidence of small-vessel ischemia in the NTG patients, but this group was also older than the controls (73 years old vs. 67 years old, respectively).

What Are the Visual Field Findings in NTG?

Visual field loss generally occurs similar to that seen in POAG.[39] However, it may appear more advanced than the amount of cupping of the nerves seen on examination.[21] Levene[3] and Greve and Geijessen[40] separately felt they found significant variations in visual field loss in patients with NTG. Defects more closely threatening fixation, relatively deeper or steeper in slope, and perhaps more frequently superior in location have been spotlighted by these authors.

In a study by Poinooswamy et al,[41] patients with NTG were noted to have defects in their visual fields that were more advanced than in patients with

high tension glaucoma (over 21 mm Hg). Within the NTG group, the patients more often presented with unilateral visual field loss. The authors also found that the left eye of the normal tension group was more likely to have a defect present compared to the right eye. Overall, the frequency of unilateral field loss between the high tension group and the normal tension group was similar (21% and 25%, respectively). The authors noted that with increasing age, the frequency of unilateral field loss decreases. They concluded that progression of the disease is not unexpected.

Crichton et al's[9] study was similar in its conclusion that, with a 2 mm Hg or greater difference between eyes, a correlation was seen with more visual field loss in the eye with higher IOP. This research also found that in several cases of asymmetric visual field loss, there was symmetric IOP.

Caprioli and Spaeth[42] showed that in NTG, one could find defects that were deeper, steeper, and closer to fixation. Levene[3] also found that fixation was threatened more often than in patients with POAG. Caprioli et al[43] compared visual field defects in POAG (high tension glaucoma) and NTG, and found that more diffuse loss was seen in younger patients with higher IOPs. In one study, 30% of 53 patients with unilateral NTG had visual field loss in the fellow eye within an average follow-up of 25 months.[44] Furthermore, the loss in the second eye was often (75%) in the same region of loss in the first eye; 88% of the losses first appeared in the paracentral region, and, overall, 69% of the losses were superior in location. Araie[45] showed no overall difference in the pattern of loss between normal tension and POAG patients.

How Should the NTG Patient Be Evaluated?

NTG is a diagnosis of exclusion. Taking the adage that "common things are common," the physician should exclude other possible etiologies of optic nerve cupping with or without visual field loss. When NTG is suspected, a comprehensive history should be taken to rule out chronic anemia, cardiopathies, acute blood loss, episodes of systemic hypotension, decreased cerebral blood flow, blood dysplasias, and neurosyphilis.

A diurnal curve should be completed before the diagnosis of NTG is affirmed. Opinions vary as to the number of specific readings, but at least three readings (early morning, noon, mid- to late afternoon) should be required. To evaluate IOP one morning and again a few months later in the afternoon is totally inadequate.

The amount of cupping should be recorded by drawing or photography. Nerve layer topography or polarimetry of the nerve fiber layer may supplement, but at this time not replace, a drawing or stereo disc photographs. These newer technologies appear to have more value in monitoring the patient for change rather than in diagnosing glaucoma.[46]

Perimetry should be performed for baseline information. An automatic static threshold perimetric test is, at present, the state of the art. Because glaucoma (POAG or NTG) is a spectrum, the cupping can be abnormal or progressive before perimetric deficits appear. Therefore, the diagnosis of NTG does not require that a visual field defect be present. Blue-yellow perimetry may be of value in detecting visual field loss before standard white-on-white testing can elicit a loss of function.

With regard to radiologic studies, computed tomography (CT) and MRI studies in an asymptomatic patient have a very low yield for finding central nervous system abnormalities. Stroman and associates at the American Academy of Ophthalmology[46] found a low incidence of intracranial lesions in patients suspected of having NTG (2 of 53 patients). This study also showed that diffuse small-vessel disease changes were more frequent in the NTG group. Based on this study, it seems that unless a patient presents with a visual field defect suggesting cerebral etiology or the patient shows progression despite apparently adequately reduced IOP (25–30%), radiologic studies need not be requested nor a neurologic consult sought.

Treatment and Management

In the face of progressive nerve cupping and/or visual field loss, the ophthalmologist should consider poor compliance and inadequate IOP control (Fig. 4–1). The physician must urge the patient to use the prescribed medication as directed. A diurnal curve should be performed to search for IOP spikes. After the data are gathered, changes in medications and surgery (laser or incisional) should be considered. Visual fields should be repeated to verify the consistency of new progression. Disc photos may need repeating to objectively compare with previous ones. The newer imaging techniques, such as HRT, scanning laser polarimetry, and ocular coherent tomography (OCT) may also have more of a role in detecting or verifying progression.

If no evidence of visual field loss accompanies a mildly increased cup-to-disc ratio, the ophthalmologist should examine siblings for the possibility of physiologic cupping. The physician may also choose to follow the suspicious patient, looking for progression, before instituting therapy.

It is my experience that most glaucoma patients prefer to try topical medications before moving on to surgery. The collaborative NTG study group has shown that reducing IOP 30% or more slows the progression of this disease.[7] It seems reasonable to set this as a goal for our patients. Although beta-blockers are the mainstay in the treatment of elevated IOP, it is often difficult to medically reduce the "normal" IOP with a single medication. Schuman et al[47] have shown that many patients presently on a systemic beta-blocker may respond in a decreased manner to topical beta-blockers. Prostaglandin analogues and α-adrenergic agonists, along with topical carbonic anhydrase inhibitors (CAIs) may be better choices in this group of patients.[47]

Laser trabeculoplasty often helps to lower IOP in NTG, but may require adjunctive medications or itself be used as an adjunctive medication. Incisional surgery has also been successful in obtaining significant reductions in IOP. The ophthalmologist may also consider other methods of improving the situation, but not necessarily decreasing the IOP in patients diagnosed with NTG. Calcium channel blockers may help improve blood flow.[14,15] Betaxolol has been shown to possibly have a similar mechanism of action in preserving visual field function while also lowering IOP.[48,49] Neuroprotection or regulation of apoptosis may be a useful tool in the near future. Brimonidine (an α-adrenergic agonist) may have the ability to upregulate "survival" signals, based on experiments in animals.[50–52]

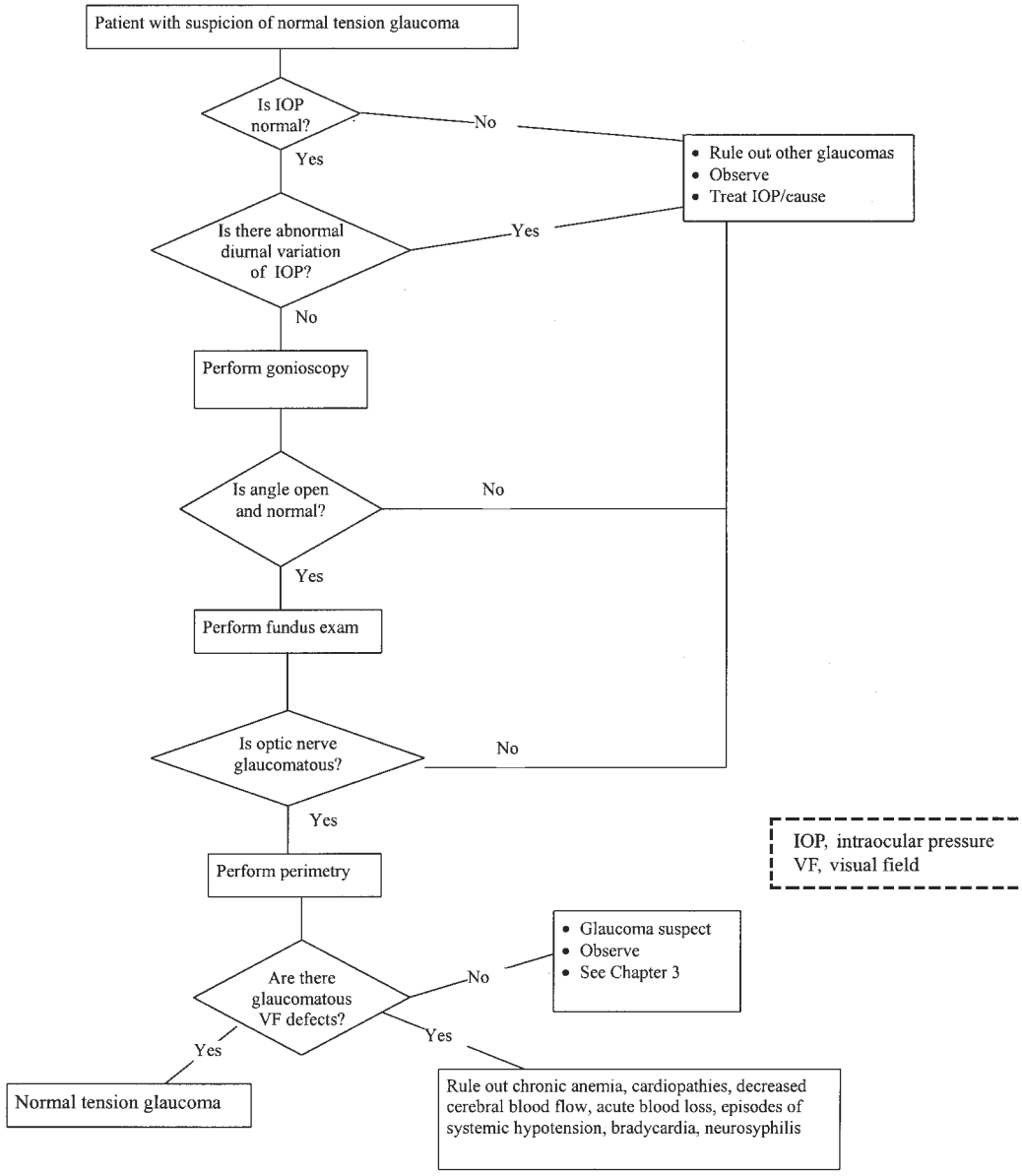

Figure 4–1. Management of a patient with suspicion of normal tension glaucoma.

Kamal and Hitchings[8] reported that 24-hour blood pressure monitoring is used in their patients who worsen despite lowering of the IOP. They look for episodes of systemic hypotension and work with the patient's family physician to try to minimize this, as well as to flatten out the diurnal variation of the IOP with topical medications.

Future Considerations

IOP that is not tolerated by the optic nerve will always be a major risk factor in glaucoma, regardless of type. Research into the factors causing "intolerable" IOP continues, with work being focused on the trabecular meshwork, immunologic status, genetic variables, blood flow, and apoptosis. Invariably, with further knowledge, distinctions between NTG and POAG will change, so that these two may become more distinct or more similar.

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◆ 5 ◆

Primary Angle-Closure Glaucoma

James A. Savage

Definition

It is not entirely clear what disease the ancient Greeks referred to as γλαυκωμα.[1] Although it is certainly likely that some of the eyes were actually glaucomatous, it was not until the early 20th century that the true nature of the family of diseases that we now call the glaucomas was recognized.

Advances in the instrumentation of ophthalmoscopy, tonometry, and gonioscopy enabled keen observers to distinguish glaucoma from other maladies of the eye and then to subdivide the glaucomas into more distinct entities. These advances culminated in the 1930s with Barkan's gonioscopic studies, which laid out the current system for classification of the glaucomas into those with open angles and those with closed angles.[2,3]

What Is Primary Angle-Closure Glaucoma?

Primary angle closure is apposition or adhesion of the iris to the trabecular meshwork as a result of crowded anterior segment anatomy in a predisposed eye. *Primary* angle closure must be differentiated from *secondary* forms of angle closure, where iris tissue blocks the angle as a consequence of another preexisting ocular disease such as neovascular glaucoma associated with diabetes or retinal vein occlusion, aphakic and pseudophakic pupillary block, uveitis, iridocorneal endothelial (ICE) syndrome, or phacomorphic glaucoma. Table 5–1 lists conditions to be considered in the differential diagnosis of secondary angle-closure glaucoma.

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Table 5–1. Differential Diagnosis of Secondary Angle Closure

Neovascular glaucoma
Central retinal vein occlusion
Uveitis
Iris bombé
Iridocorneal endothelial (ICE) syndrome
Following scleral buckling or panretinal photocoagulation
Malignant (ciliary block) glaucoma/aqueous misdirection
Ciliary body swelling, inflammation, or cyst
Phacomorphic glaucoma
Subluxated lens
Nanophthalmos
Posterior segment tumors

Under What Circumstances Does Primary Angle Closure Occur? What Are Its Underlying Mechanisms?

Relative Pupillary Block

Relative pupillary block is, by far, the most common of the two mechanisms for primary angle closure.[4] Predisposed eyes are usually small and hyperopic with crowded anterior segments. In such eyes, the contact between the lens and iris at the pupil is more snug than normal, as shown in Figure 5–1A. This lens–iris contact tightens with the enlargement of the crystalline lens as a normal consequence of aging. In predisposed eyes, at a critical pupillary diameter (4–6 mm), the resistance to the flow of aqueous from posterior chamber through the pupil and into the anterior chamber, called relative pupillary block, causes fluid pressure to build behind the iris as shown in Figure 5–1B. This pressure differential pushes the peripheral iris forward into the angle, against the trabecular meshwork, causing appositional and eventually permanent synechial angle closure, as illustrated in Figure 5–1C. As a result, the intraocular pressure (IOP) rises.

The possibility of inducing acute angle closure with pharmacologic mydriasis has contributed to a reluctance among primary care physicians to dilate the pupil for diagnostic ophthalmoscopy. In a predominantly black and Caucasian population, the risk of inducing angle closure by dilating the pupil is less than 1% and is approximately 0.3% if patients are screened for family history of glaucoma and for shallow anterior chamber with a penlight.[5] The recognition of retinal disorders is greatly enhanced by mydriasis. Therefore, it would appear that the benefits of earlier detection of such a common blinding condition as diabetic retinopathy alone outweigh this small risk of angle closure from pharmacologic mydriasis.

Obviously, a peripheral iridectomy, as shown in Figure 5–2, eliminates relative pupillary block by providing an alternative route for aqueous to flow from the posterior chamber into the anterior chamber, thereby equalizing the pressure difference between the two. This allows the iris to fall away from the angle structures, relieving the angle closure in areas where it has not yet become synechially attached to the trabecular meshwork.

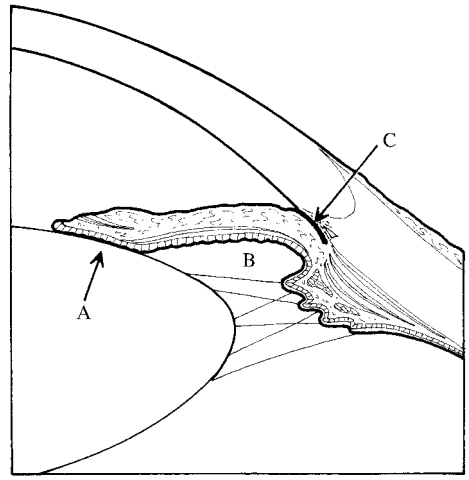

Figure 5–1. Relative pupillary block: snug iridolenticular contact at the pupil (A) with resultant increased fluid pressure in the posterior chamber relative to the anterior chamber (B) pushes the peripheral iris forward, against the trabecular meshwork, closing the angle (C). (Modified from Shields MB: Textbook of Glaucoma, 4th ed. Baltimore: Williams & Wilkins, 1998:178.)

Plateau Iris Syndrome

Plateau iris syndrome is a much less common mechanism for primary angle closure than relative pupillary block and is not affected by iridectomy.[6–9] Thus, it is imperative that all eyes with primary angle-closure glaucoma be examined gonioscopically after iridectomy, to be certain that persistent angle closure/closability from plateau iris syndrome, as shown in Figure 5–3C, is not overlooked.

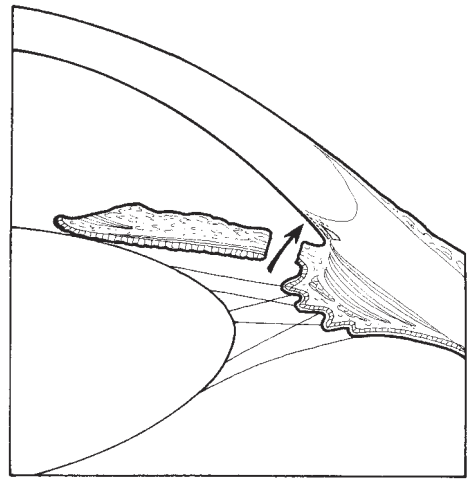

Figure 5–2. Relief of relative pupillary block with iridectomy by providing an alternate pathway for aqueous to flow from posterior to anterior chamber (*arrow*). With fluid pressure equal in posterior and anterior chambers, the iris falls away from the angle in areas where it is not yet synechially attached. (Modified from Shields MB: Textbook of Glaucoma, 4th ed. Baltimore: Williams & Wilkins, 1998:188.)

As the name suggests, the iris plane in plateau iris is flat and not convex. As a result, the axial anterior chamber depth is normal, or nearly so, whereas the peripheral iris contour is abnormally convex and lies in close proximity or is apposed to the trabecular meshwork, as shown in Figure 5–3A. When the pupil dilates in such an eye, iris tissue is pushed against the trabecular meshwork, closing the angle. Ultrasound biomicroscopic studies have shown that the underlying anatomic mechanism for plateau iris is abnormally anteriorly placed ciliary processes.[6,9] These ciliary processes, which lie just underneath the peripheral iris roll, cause plateau iris by holding the peripheral iris forward, even after iridectomy. Because plateau iris syndrome has nothing to do with resistance to flow of aqueous through the pupil, iridectomy does nothing to resolve it.

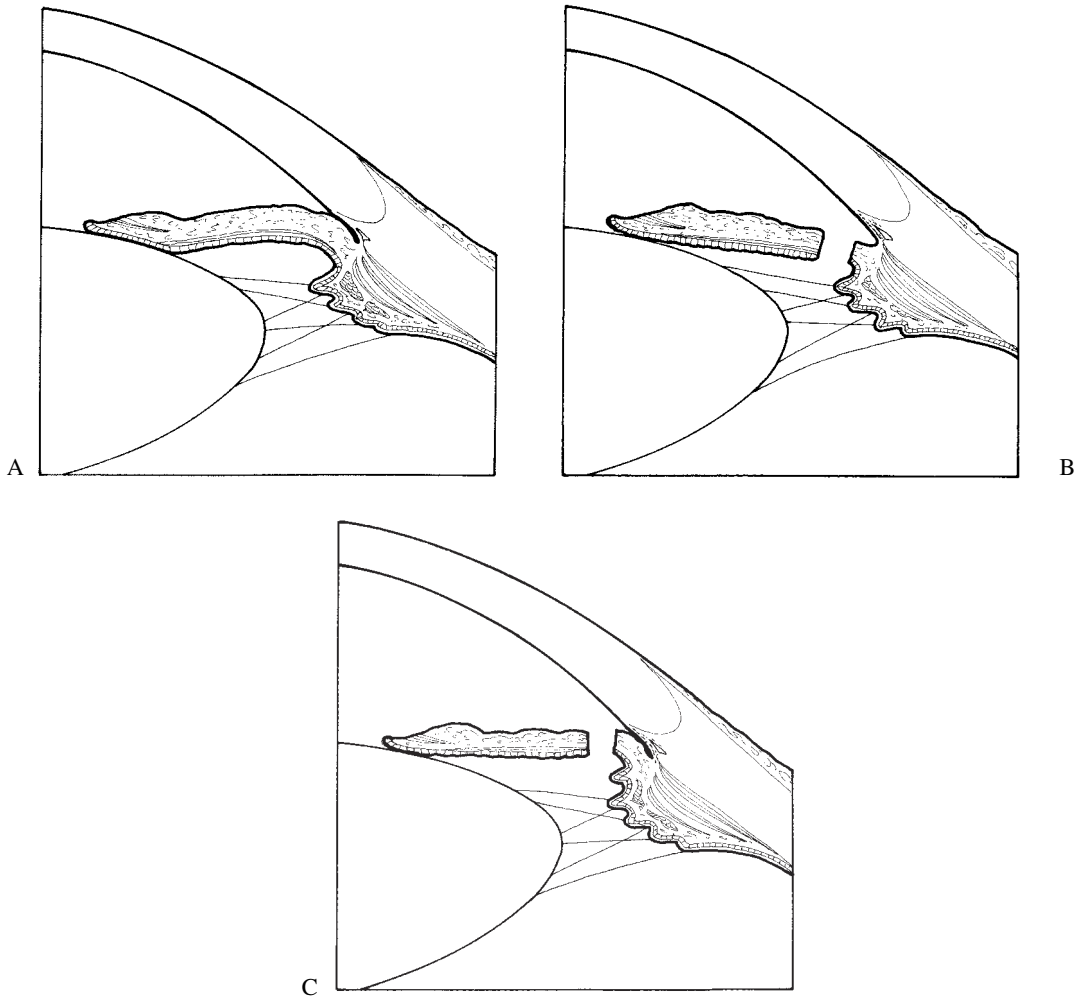

Figure 5–3. Plateau iris configuration and syndrome (A) In most eyes with an iris in plateau configuration, this is the appearance of the iris prior to iridectomy. (B) The predominant mechanism for angle closure is actually relative pupillary block and is therefore relieved by iridectomy. (C) In those rare cases where angle closure/closability persist after iridectomy, the term *plateau iris syndrome* is used. (Modified from Shields MB: Textbook of Glaucoma, 4th ed. Baltimore: Williams & Wilkins, 1998:179.)

Terminology can be confusing, but is useful and important. When a plateau-like iris is observed with slit-lamp biomicroscopy and gonioscopy prior to iridectomy, as shown in Figure 5–3A, it is termed *plateau iris configuration*. Despite this appearance of the iris and chamber angle, and the surgeon's suspicion that iridectomy may fail to open the angle, relative pupillary block is usually the predominant mechanism for the angle closure in a majority of these eyes and, as illustrated in Figure 5–3B, iridectomy is curative of the angle closure stimulus. If plateau iris and angle closability persist after iridectomy, this rare situation, shown in Figure 5–3C, is termed *plateau iris syndrome*. Plateau iris syndrome is rare, but should be ruled out following iridectomy in all eyes with primary angle closure. In addition, the surgeon should have a heightened index of suspicion for the presence of plateau iris in younger and/or myopic patients with primary angle closure.

Although it is usually detected during gonioscopy shortly after iridectomy, plateau iris syndrome may also appear years later. For this reason, careful gonioscopy should be performed periodically for the remainder of the patient's life after iridectomy for primary angle closure, to detect progressive closure/closability of the angle due to plateau iris syndrome. The plateau iris syndrome may vary in its anatomic degree, depending on the physical height of the iris plateau relative to the adjacent angle structures. If the plateau is opposite the anterior trabecular meshwork or Schwalbe's line, when the angle is crowded, the trabecular meshwork is obstructed and the IOP rises. However, in some cases the plateau may only be as high as the scleral spur or posterior trabecular meshwork so that angle crowding does not cause trabecular obstruction and elevated IOP.

Epidemiology and Importance

What Factors Anatomically Predispose Eyes to Primary Angle Closure?

Age

The prevalence of increased relative pupillary block and primary angle closure increases with age, in tandem with the natural increase in volume of the crystalline lens and decrease in resting pupil diameter. The prevalence of primary angle-closure glaucoma peaks in the sixth decade, earlier than with primary open-angle glaucoma.

Race

Among Caucasians, 75 to 90% of glaucoma cases are due to primary open-angle glaucoma, affecting 0.5 to 2.16% of the adult population.[10] This is in sharp contrast to the much lower prevalence of primary angle-closure glaucoma in this population, ranging from 0.09 to 0.17%. Population-based studies demonstrate that this relationship is reversed in Eskimos: 2.12 to 2.9% for primary angle-closure glaucoma compared to 0.01 to 0.4% for primary open-angle glaucoma.[11–16] The prevalence of primary angle-closure glaucoma is 20 to 40 times higher among Eskimos than Caucasians.

Primary angle-closure glaucoma in Asian populations has also been studied, albeit less extensively than in Eskimos. It appears that the prevalence of primary angle-closure glaucoma among Asians is intermediate between that in Caucasians and Eskimos. It has been estimated that primary angle-closure glaucoma affects more than 30 million people worldwide, at least as many as primary open-angle glaucoma.[17]

Primary angle closure is less common in blacks than Caucasians. When angle closure does occur in black patients, the chronic form is the most common.

Sex

Primary angle closure in Caucasians and especially among Eskimos, is more common in females, perhaps due to a smaller anterior segment. In black patients, the incidence of primary angle closure is equal in males and females.

Refractive Error

Refractive error definitely influences the likelihood of primary angle closure. Because hyperopes have smaller anterior segments than emmetropes or myopes, increased relative pupillary block and primary angle closure are more common in hyperopic eyes. In myopic eyes with primary angle closure, especially in younger patients, plateau iris syndrome should be suspected as a mechanism.

Family History

Primary angle closure is believed to be inherited in some cases, although a positive family history does not predict the likelihood of a future attack of acute angle-closure glaucoma.

How Is Gonioscopy Most Effectively Used in the Diagnosis and Management of Primary Angle Closure?

Gonioscopy should be performed on all patients with glaucoma, on all glaucoma suspects, and on all individuals suspected of having narrow angles. Without it, identification of the underlying mechanism and therefore the appropriate treatment of any glaucomatous condition is impossible. Skillful gonioscopy is important in the diagnosis of glaucoma, but also in its treatment, for example, in performing laser trabeculoplasty and laser gonioplasty.

Visualization of the angle structures requires a contact lens. Table 5–2 lists the common gonioscopic techniques with their respective advantages and disadvantages.

Koeppe Gonioscopy

Koeppe gonioscopy is a direct method of visualizing the chamber angle by using a dome-shaped goniolens, an illumination system, and a hand-held biomicroscope.

Table 5–2. Gonioscopic Techniques

	Direct	Indirect	
	Koeppe	**Goldmann**	**Indentation**
Advantages			
	An erect and panoramic view of the angle with excellent perception of spatial relationships, albeit with less magnification than with Goldmann or Zeiss methods; in this regard, Koeppe gonioscopy is analogous to indirect ophthalmoscopy	Greater visibility of detail because of higher magnification than with the Koeppe technique (analogous to direct ophthalmoscopy)	
		Less time-consuming than Koeppe gonioscopy	
		Instrumentation more popular and readily available than with the Koeppe technique	
	Minimal or no distortion of the chamber angle since the goniolens rests over a wide area posterior to the limbus		
	Can be performed on both eyes simultaneously, to enable the examiner to appreciate subtle differences between the angles of the two eyes	Ease in learning technique	Enables differentiation between appositional and synechial angle closure
			No coupling solution necessary
Disadvantages			
	Difficulty in learning the technique	For the same reason that indentation (Zeiss, Posner, Sussman, etc.) goniolenses are useful in dynamic gonioscopy to differentiate appositional (reversible) vs. synechial (permanent) angle closure, they may be undesirable for estimating the depth of the chamber angle in its resting state; artifactual deepening of the anterior chamber during gonioscopy by the inadvertent application of pressure with an indentation goniolens upon the central cornea may lead the examiner to underestimate the narrowness and closability of the angle in its natural state; on the other hand, gonioscopy with a Goldmann lens can occasionally mislead the examiner into overestimating the narrowness of the angle width because of artifactual angle narrowing from pressure on the limbus from the goniolens	
	Expensive instrumentation		
	Less magnification, so less detail visible than with indirect techniques		
		Indirect gonioscopy provides a less panoramic view of the angle than Koeppe gonioscopy, which can make appreciation of spatial relationships of angle structures more difficult	
		Tendency to overestimate narrowness of angle	Proper technique requires practice
			Tendency to underestimate narrowness of the angle

Goldmann and Indentation Gonioscopy

Goldmann and indentation gonioscopy are indirect methods of visualizing the chamber angle in the mirror of a gonioprism with a slit-lamp microscope. Indirect gonioscopy provides an inverted image, but the right-left and up-down orientations are maintained.

What Questions Should Be Answered with Gonioscopy in Primary Angle-Closure Glaucoma?

Three questions should be answered with gonioscopy when evaluating a patient for angle closure:

Is the Angle Open or Closed in Its Natural Position?

The ideal method of observing the angle in its natural position is Koeppe gonioscopy.[18] However, special instruments are required and so, from a practical point of view, indirect gonioscopy is more convenient for most ophthalmologists. Clinicians should use the method with which they are most comfortable and confident. The avoidance of artificial distortion of the angle during gonioscopy, especially with indentation lenses, is crucial to the evaluation of the natural position of the angle.

If Angle Closure Exists, Is It Appositional (Reversible) or Synechial (Permanent)?

Indentation gonioscopy, as described by Forbes,[19,20] is a technique wherein one uses a contact lens (Zeiss, Posner, Sussman, etc.) with a small area of corneal contact to push aqueous from the central to peripheral anterior chamber to artificially open the angle. Areas of appositional closure of the angle, in which the peripheral iris is resting upon but is not yet adherent to the trabecular meshwork, can be opened by moving the iris away from the angle structures with this dynamic indentation gonioscopy. This maneuver brings into view any peripheral anterior synechias where the iris is adherent to the angle.

The extent of synechial versus appositional closure is of critical importance because, following relief of relative pupillary block with iridectomy, the control of intraocular pressure will depend on the fraction of trabecular meshwork circumference not yet closed with synechias. Areas of synechial closure remain closed following relief of the angle closure mechanism and are therefore permanently unavailable for aqueous outflow except in certain cases of acute angle closure where fresh peripheral anterior synechias can be successfully broken with laser gonioplasty or surgical goniosynechialysis.[21–23] The extent of appositional versus synechial angle closure was a much more serious issue prior to the introduction of laser iridectomy, when surgical peripheral iridectomy was required to relieve pupillary block. In cases where surgical iridectomy failed to control the IOP, a second trip to the operating room for a filtration operation was then necessary.

If Open, Is the Angle Closable?

It is not always possible to determine with gonioscopy if an angle is definitely closable. The examiner's judgment and experience play a large role. In this situation, one is left with the option of proceeding with laser iridectomy or using other criteria, such as provocative testing, to try to assess the risk of future angle closure.

What Role, If Any, Does Provocative Testing Play in the Management of Primary Angle-Closure Glaucoma?

Provocative testing has little, if any, role. Before the availability of modern laser iridectomy techniques, the relief of pupillary block required a surgical iridectomy. Although relatively safe, this procedure poses the usual uncommon but unavoidable risks of intraocular surgery. In the past, to minimize unnecessary surgical iridectomies, provocative tests were employed to try to estimate the closability of the angle in a particular eye by inducing angle closure artificially. Although provocative tests are rarely used today, it is useful to be aware of their existence and physiologic bases.[24–26]

The ideal provocative test for angle closure would be physiologic, simple, not time-consuming, reproducible, and safe. No provocative test meets all of these criteria. A positive provocative test is no guarantee that a patient will indeed develop angle closure, just as a negative test does not assure immunity from a subsequent angle closure attack. Why, then, should one bother with provocative testing? These tests can be used as adjuncts to bolster one's clinical impression, and they are useful in the rare circumstance where laser iridectomy is unavailable or not possible. Ultimately, the decision to treat an asymptomatic patient with laser iridectomy because of narrow angles rests on the clinical judgment of the ophthalmologist. If the ophthalmologist decides that laser iridectomy is not necessary in a patient with narrow angles, the patient should be alerted to the symptoms and dangers of acute and subacute angle closure and should have periodic examinations including careful gonioscopy. The role of provocative testing in answering the question of closability of the angle is minor, especially when one considers the availability and safety of modern laser iridectomy.

Diagnosis and Differential Diagnosis

How Does the Patient with Primary Angle Closure Present to the Ophthalmologist?

Primary angle closure presents one of three clinical pictures: acute, subacute, or chronic:

Acute Primary Angle-Closure Glaucoma

Acute angle-closure glaucoma presents as an emergency with abrupt onset and rapid elevation in IOP. The striking signs and symptoms are listed in Table 5–3. The differential diagnosis of acute primary angle-closure glaucoma, as shown

Table 5–3. Signs and Symptoms of Primary Acute Angle-Closure Glaucoma

Signs	Symptoms
Significant elevation of intraocular pressure (IOP) The very high pressure suppresses aqueous production; as a result, the pressure is often subnormal for a variable period of time following relief of the acute angle closure attack, even if much of the angle is permanently closed with synechiae The likelihood of an unfavorable outcome is not proportional to the severity of IOP elevation during the attack Hyperemic eye Fixed, mid-dilated pupil (commonly vertically oval) Steamy cornea (epithelial edema due to elevated IOP) Anterior chamber flare and cells (may have "pseudo KPs," but never true keratatic precipitates) Shallow *peripheral* anterior chamber (van Herick et al[28]); axial depth of the anterior chamber varies with the mechanism of angle closure, e.g., shallow with malignant glaucoma or nanophthalmos, deeper with relative pupillary block and normal or nearly so with plateau iris Gonioscopy: the diagnosis of acute angle closure requires gonioscopic confirmation of a closed angle; if the cornea is too hazy for visualization of the angle structures, topical glycerin may help to clear epithelial edema and permit examination of the angle Important: remember to perform gonioscopy on the *fellow* eye since primary angle closure is almost always bilateral; if the angle in the fellow eye is wide open, suspect a diagnosis other than primary angle closure such as neovascular, uveitic, or phacomorphic glaucoma (see Table 5–4) Indentation, "dynamic," or "compression" gonioscopy with a Zeiss, Posner, Sussman, or another similar lens can be used to assess the extent of synechial (permanent) versus appositional (reversible) angle closure; this provides a clue as to the fraction of the angle that will open when the mechanism for angle closure is eliminated, usually with iridectomy; compression gonioscopy is also therapeutic for an acute attack (it pushes aqueous from the central to peripheral anterior chamber, which temporarily opens the angle so that aqueous can reach the trabecular meshwork and escape from the eye) Sector gray atrophy of the iris stroma; rarely, this atrophy can cause a spontaneous and lasting cure of angle closure by altering of the lens/iris interface, relieving relative pupillary block Glaukomflecken (permanent whitish anterior lens opacities, which are evidence of an existing or prior acute elevation in IOP)	The headache and nausea of acute angle closure often masquerade as a nonocular medical illness, the negative workup of which delays diagnosis and treatment of the angle closure attack, thereby increasing the chances of a poor outcome Pain (browache) Decreased visual acuity, especially characterized by colored rainbows around lights due to epithelial corneal edema Nausea and vomiting Diaphoresis

Table 5–3. Continued

Signs	Symptoms
Disc hyperemia and edema early in the acute attack, the disc becomes atrophic later, with the extent of pallor often outweighing that of cupping	
Nonspecific visual field constriction, which is occasionally reversible, especially in younger patients	
Bradycardia	

in Table 5–4, must be considered. Uveitic, neovascular, and other secondary acute glaucomas can mimic primary angle closure and lead to incorrect diagnosis and inappropriate treatment.

Subacute (Intermittent, Prodromal, or Subclinical) Primary Angle-Closure Glaucoma

Subacute angle closure is characterized by periodic and self-limited attacks of mild ocular pain and blurred vision.[27] The history provided by the patient is often vague, but the examiner should listen carefully. Complaints of colored rainbows around lights, signifying corneal edema, should automatically trigger a gonioscopic examination, even if the IOP is normal and the angle seems deep upon slit-lamp examination. These rainbows differ from the monochromic halos around lights of which a patient with cataract might complain. Halos are not due to corneal edema, and therefore are not colored. Symptoms of subacute angle closure are typically greatest in the evening and usually improve by morning, presumably due to lessening of angle closure from the miosis of sleep. Because subacute angle closure can progress to acute or chronic angle closure, it is important to suspect it and perform gonioscopy on all patients giving a peculiar history of intermittent eye or brow discomfort or dull ache, blur, or transient monocular visual loss, even if the peripheral anterior chamber appears deep upon slit-lamp examination. The slit-lamp examination can mislead the examiner into assuming, incorrectly, that the angle is open. If

Table 5–4. Differential Diagnosis of Acute Primary Angle-Closure Glaucoma

Anterior uveitis
Neovascular glaucoma
Iridocorneal endothelial (ICE) syndrome
Central retinal vein occlusion
Ciliary body swelling, inflammation or cysts
Following scleral buckling or panretinal photocoagulation
Malignant (ciliary block) glaucoma/aqueous misdirection
Phacomorphic glaucoma
Subluxated lens
Phacolytic glaucoma
Nanophthalmos
Posterior segment tumors

angle closure is allowed to continue undetected, progressive irreversible synechial angle closure will result. This condition often leads to a glaucomatous situation no longer manageable with laser iridectomy, but only with filtration surgery.

Chronic Primary Angle-Closure Glaucoma

Chronic angle closure has no symptoms. It develops over a long period of time, occasionally in patients with preexisting primary open-angle glaucoma. Therefore, it is essential that all glaucoma patients have initial and periodic gonioscopy, no matter how deep the peripheral anterior chamber appears at the slit lamp. When the IOP control in a patient being treated for chronic open-angle glaucoma becomes more difficult than previously, gonioscopy may reveal that chronic angle closure has begun, with varying amounts of appositional and/or synechial closure. In a predisposed, usually hyperopic, eye, as the patient ages and the crystalline lens enlarges, relative pupillary block increases, which can cause slowly progressive angle closure. This situation is occasionally discovered at the time of laser trabeculoplasty that has been scheduled for what is believed to be uncontrolled open-angle glaucoma. In such cases, laser iridectomy is necessary to relieve pupillary block and interrupt the progression of permanent synechial angle closure. Following the elimination of the underlying cause of the angle closure, medical therapy, laser trabeculoplasty, or surgical therapy are employed, as needed, for IOP lowering.

The depth of the peripheral anterior chamber as visualized at the slit lamp, although very useful in most cases for estimating the closability of the angle, can be very misleading and must not take the place of careful gonioscopy.[28] Unless careful gonioscopy is periodically performed on all glaucoma patients, the assumption that an angle, based on the slit-lamp examination, is open and not closable can lull the ophthalmologist into a dangerously false sense of security. In the early stages of chronic angle-closure glaucoma, permanent synechial angle closure can progress despite normal IOP, especially if aqueous suppressant therapy, such as carbonic anhydrase inhibitors or topical beta-blockers, are used. Eventually, a critical fraction of the circumference of the trabecular meshwork becomes permanently closed with synechias. At this point, the remaining fraction of the angle that is still open provides insufficient facility of outflow to keep pace with aqueous production, and the IOP rises. In many such cases, following relief of pupillary block with iridectomy, the pressure remains high despite medications and laser trabeculoplasty, and filtration surgery is required. In chronic primary angle-closure glaucoma, even if glaucoma medications successfully lower the IOP, laser iridectomy is necessary to preserve that portion of the angle not yet closed with peripheral anterior synechias. It is very difficult to predict in which cases of primary angle closure the IOP will be controlled with iridectomy alone, and which cases will require filtration surgery. Because laser iridectomy is relatively safe compared to filtration surgery, it should be performed, if possible, in all cases. Then if the IOP remains unacceptably high,

despite the maximum benefit from glaucoma medications and laser trabeculoplasty to the remaining open angle, surgery can be performed.

Treatment and Management

How Is Primary Angle Closure Treated?

The first goal in the management of primary angle closure is to eliminate relative pupillary block with an iridectomy. The initial evaluation of primary angle closure and its management is depicted in Figure 5–4, culminating in laser iridectomy. In the case of acute angle closure, the cornea is often too edematous to permit laser. One must first break the attack medically to allow the cornea to clear. Acute angle closure is an emergency and must be resolved quickly to protect the optic nerve from pressure-induced damage and to prevent permanent synechial angle closure. Then, once iridectomy has eliminated relative pupillary block, the patient must be carefully reevaluated for the important, but often neglected, management necessary after iridectomy, which is diagrammed in Figure 5–5.

How Is an Attack of Acute Primary Angle Closure Treated?

Medical Therapy

Drugs that are useful in the treatment of acute angle closure glaucoma are listed in Table 5–5.

Hyperosmotic Drugs Hyperosmotics are the cornerstone of medical therapy for acute angle-closure glaucoma. Because they lower the IOP by shrinking the volume of the vitreous, hyperosmotics work independently of neuromuscular action of the iris and of the production of aqueous. Until iris muscular paralysis due to pressure-induced ischemia is relieved by the lowering of IOP provided by hyperosmotic drugs, pilocarpine, a direct parasympathomimetic, cannot stimulate the pupillary sphincter to cause needed miosis. Also, since the production of aqueous humor is significantly depressed by the acute pressure elevation, aqueous suppressants such as beta-blockers and carbonic anhydrase inhibitors, although helpful, cannot by themselves break an acute attack.

If at all possible, the patient should have nothing to eat or drink prior to the administration of hyperosmotics and for 2 hours afterward. Ice chips can be given for thirst, if necessary. In addition, oral hypersomotics commonly cause nausea and occasional vomiting in the already ill patient. This can interfere with their administration and retention. Injectable antiemetic medication can be useful in this situation. The patient should be observed closely and not discharged from the office immediately after hyperosmotics. Possible side effects are headache, confusion, cardiac arrhythmia, and subdural or subarachnoid hemorrhage.

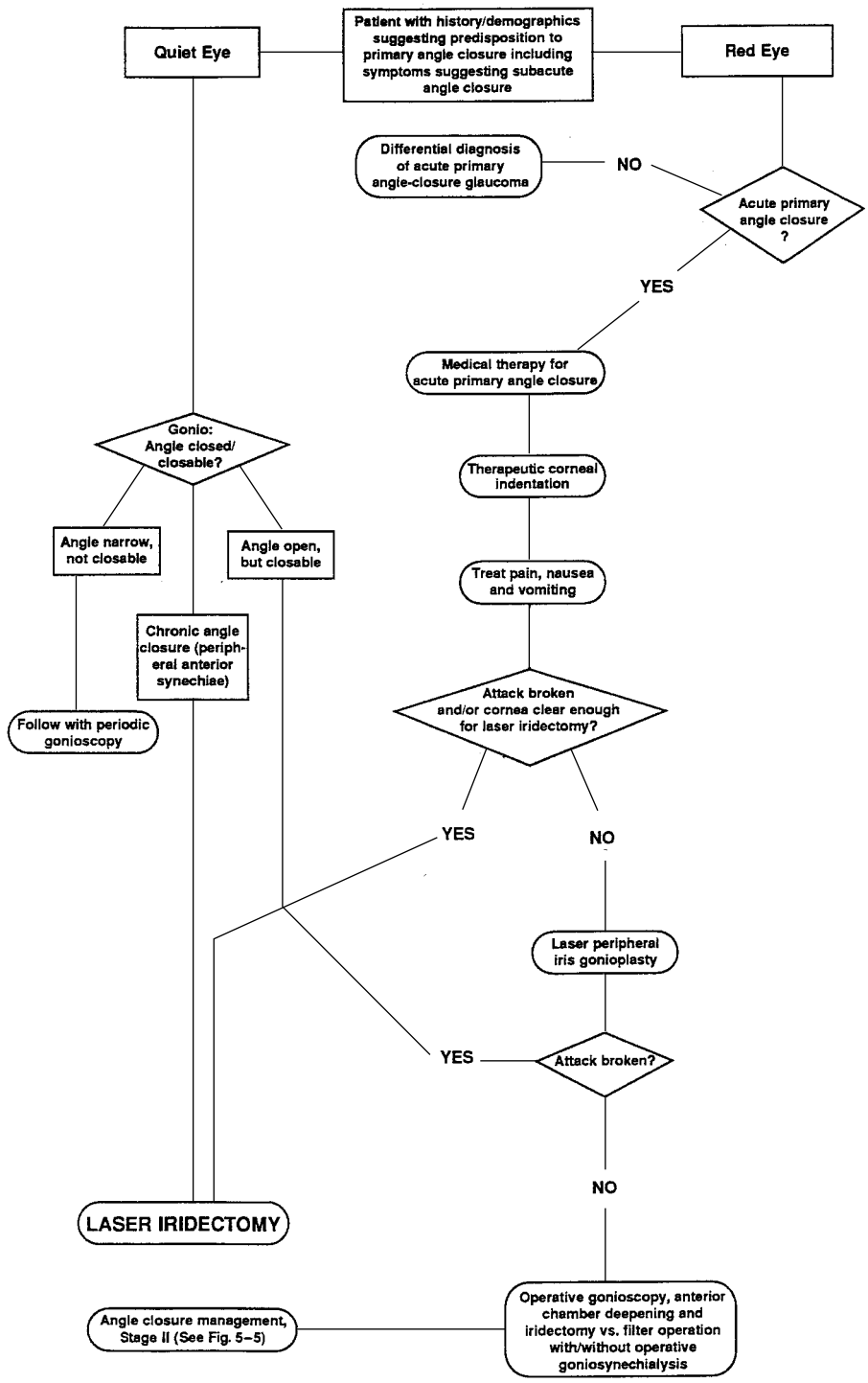

Figure 5–4. Strategy for medical and other initial therapy for primary angle-closure glaucoma, culminating in laser iridectomy.

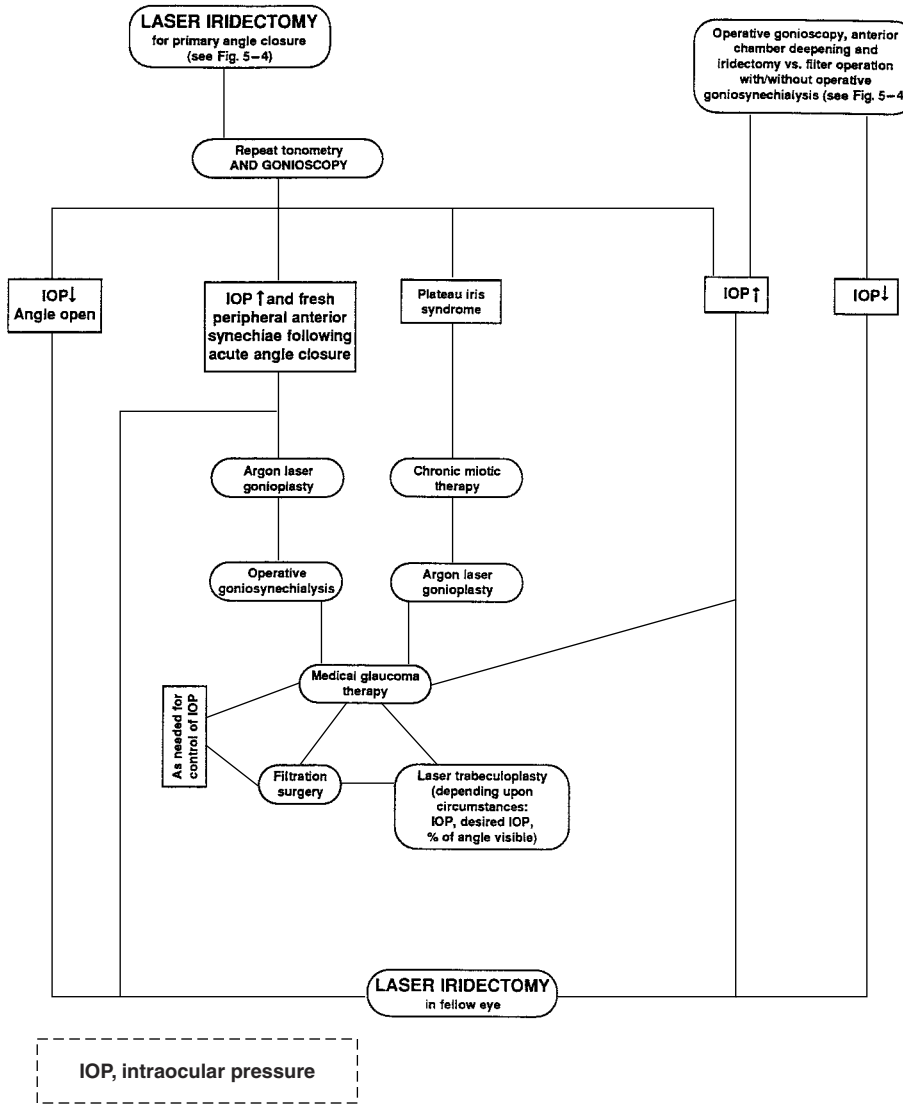

Figure 5–5. Decision tree: strategy for therapy of primary angle-closure glaucoma after iridectomy has eliminated relative pupillary block.

Other Medications

Miotics[29,30,31,32], beta-blockers, carbonic anhydrase inhibitors, and alpha agonists are described in Table 5-5.

Therapeutic Corneal Indentation

Indentation of the anesthetized central cornea with a sterile cotton-tipped applicator, indentation goniolens (Zeiss, Posner, or Sussman), or applanation

Table 5–5. Medical Therapy for Acute Angle-Closure Glaucoma

A. Hyperosmotics
   1. Oral hyperosmotics
      a. Isosorbide (Ismotic) 45%
         Contributes to the tonicity of the blood and is excreted unchanged in the urine; therefore, no caloric problem for diabetics
         Other side effects are less than with glycerin
         Dosage = 1.5 g/kg ≅ 1.5 mL/lb ≅ 3 mL/kg (therefore, one 220-mL bottle for a 70-kg/154-lb adult)
      b. Glycerin (Osmoglyn) 50%
         Metabolized before excretion (calories for diabetics)
         Dosage = 2–3 mL/kg or 140–210 mL for a 70-kg/154-lb adult
   2. Intravenous hyperosmotics
      Mannitol 20–25%
         Dosage = 1-2 g/kg (e.g., a 50–100 cc bolus of 20–25% solution intravenously, over 20 minutes for a typical adult)
         This bolus is as effective as a slow drip of greater volume of lower concentration of mannitol solution

B. Miotics
   1. Pilocarpine 2% every 30 minutes in the affected eye (2% solution is as effective as higher concentrations with less risk of cholinergic toxicity from repeated administration); because pilocarpine is a direct parasympathomimetic, it does not influence the iris sphincter musculature until hyperosmotic drugs and/or therapeutic corneal indentation have lowered the intraocular pressure (IOP), which, in turn, relieves the iris ischemia
   2. Thymoxamine[31,32] (not available in the U.S.) and dapiprazole[29,30] (Rev-Eyes) are α-adrenergic blockers that produce miosis by relaxing the iris dilator muscle (this is a theoretical advantage over pilocarpine, which stimulates the iris sphincter and ciliary muscle and moves the lens/iris diaphragm forward, further shallowing the anterior chamber)
   3. Strong miotics: indirect parasympathomimetics (phospholine iodide, Humorsol) are contraindicated for primary angle closure because they produce iris congestion, can worsen pupillary block, and can enhance formation of peripheral anterior synechiae

C. Topical beta blockers
   Be careful of systemic side effects and overdosage; use lacrimal occlusion and do not exceed the maximum recommended 12-hour frequency of administration
   Cosopt, a combination of timolol and dorzolamide in a single drop, simplifies therapy if both beta-blockers and topical carbonic anhydrase inhibitors are desired simultaneously

D. Carbonic anhydrase inhibitors (CAIs)
   1. Topical CAIs
      Dorzolamide 2% (Trusopt) alone or in combination with timolol maleate in Cosopt
      Brinzolamide 1% (Azopt)
   2. Oral and Parenteral CAIs
      Acetazolamide (Diamox or AK-Zol) 250–500 mg orally (intramuscular or intravenous, if the patient is nauseated)
      Methazolamide (Neptazane) 25–100 mg orally

E. Alpha agonists
   1. Apraclonidine 0.5% or 1% (Iopidine)
   2. Brimonidine 0.2% (Alphagan)

prism (on 20 seconds, off 10, on 20, etc.) can be invaluable in breaking an acute attack of primary angle-closure glaucoma.[33] Therapeutic corneal indentation works by the same principle as diagnostic indentation gonioscopy. The pressure applied to the central cornea pushes aqueous from the central anterior chamber into the peripheral anterior chamber, which opens the angle and allows aqueous to reach the trabecular meshwork. A variation on this theme was described by Kimbrough et al,[34] who reported the successful relief of acute angle closure with adjunctive retrobulbar anesthesia followed by intermittent application of the "super pinkie" ocular compression device.

Pain, Nausea, and Vomiting

Medical therapy should be provided.

Laser Peripheral Iris Gonioplasty

Argon laser photocoagulation can be used to shrink and flatten the peripheral iris to open the angle in attacks of acute angle-closure glaucoma that fail to respond to medications and corneal indentation.[35,36] Often, the cornea is not sufficiently transparent to perform definitive laser iridectomy, but is clear enough to permit the application of laser energy to shrink the peripheral iris. In this situation, gonioplasty can be employed to open some or all of the angle to lower the IOP and clear the cornea, making subsequent laser iridectomy possible. The effect of gonioplasty is often transient and therefore is not a substitute for definitive relief of relative pupillary block with iridectomy. Similarly, attempted argon laser iridectomy, even in the absence of patency, can inadvertently "peak" the pupil in the meridian toward the laser iridectomy site, transiently relieving relative pupillary block, and breaking the acute angle-closure attack. For this reason, care must be taken to be certain that the iridectomy is patent. If it is not, the iridectomy must be completed because the transient pupilloplasty effect will usually lessen with time and eventually predispose the eye to recurrence of angle closure. In addition to its value in treating an acute attack of angle closure, argon laser gonioplasty has several other valuable uses in the management of primary angle closure as listed in Table 5–6.

What Should Be Done If the Acute Attack of Angle Closure Is Unresponsive to Medical Therapy and Laser Gonioplasty, and the Cornea Is Not Sufficiently Clear to Allow Laser Iridectomy?

In this situation, surgical iridectomy is required. The question is, Will iridectomy alone resolve the problem or should a filtration operation be performed? Before the availability of laser iridectomy, this was a common dilemma for the ophthalmologist confronted with acute angle closure. It is unpleasant for both the patient and the surgeon to have to follow one intraocular surgical pro-

Table 5–6. Argon Laser Gonioplasty: Indications

Indications	
During an acute attack of primary angle-closure glaucoma, when the cornea is not sufficiently clear to allow laser iridectomy, gonioplasty can occasionally be used to open segments of the angle to help lower the pressure and clear the cornea permit definitive treatment (laser iridectomy)	
Following laser iridectomy for acute angle-closure glaucoma, gonioplasty can be used to break fresh peripheral anterior synechiae to open the angle	
Following laser iridectomy, when appositional angle closure/closability persists in the form of plateau iris syndrome, gonioplasty can be used to remove the peripheral iris roll from the vicinity of the trabecular meshwork; retreatment is often necessary; the patient should be followed with periodic gonioscopy indefinitely	
Gonioplasty can be used to preserve open angle in concert with laser iridectomy in nanophthalmic eyes; these laser options are especially important because intraocular surgery in nanophthalmos is fraught with danger	
Gonioplasty laser settings	
Spot size:	200 μm increasing to 500 μm
Duration:	0.2 seconds increasing to 0.5 seconds
Power:	50 mW increasing to 400 mW
Number:	6–15 evenly spaced burns per quadrant
Use the lowest settings needed to achieve a moderate stromal burn and shrinkage of tissue and the desired anatomic result	
Use of three-mirror lens is optional but preferred	
Treat *less* than the entire circumference of available angle in eyes where inflammation and debris might cause a dangerous pressure spike and damage a cupped and vulnerable optic nerve	

cedure with another. When surgical peripheral iridectomy becomes necessary, operative anterior chamber deepening and gonioscopy allows quantification of permanent synechial angle closure in the operating room, where the decision between iridectomy and filtration surgery can be weighed.[37,38] Also, at that time, operative goniosynechialysis can be used to break fresh peripheral anterior synechias to restore angle anatomy and aqueous outflow.[21,22] Although operative goniosynechialysis has been successfully employed up to 1 year following acute angle closure, the earlier one can open and restore the functional anatomy of the angle, the better. Depending on how much of the angle is not yet closed with synechias, a decision must be made whether to perform iridectomy alone or as part of a filtration operation. Chandler and Simmons[37] have recommended filtration surgery if more than 6 clock hours of angle are closed with synechias; surgical peripheral iridectomy alone if 4 or less clock hours are closed; and that the surgeon use his own judgment for eyes with 4 to 6 clock hours of synechial angle closure. These recommendations, although very helpful, are not foolproof. Mixed mechanism glaucoma may be present with very poor facility of outflow and high pressure, even with an entirely open angle. If, following surgical iridectomy, the IOP remains uncontrolled; glaucoma medications, laser trabeculoplasty, and glaucoma filtration surgery must be employed, as needed, to control any residual glaucoma at an acceptable level of IOP.

What Should Be Done After Breaking the Attack of Acute Angle Closure?

When the acute attack is broken or the cornea is sufficiently clear, proceed with laser iridectomy to eliminate pupillary block and prevent its recurrence and angle closure.[39–41] Remember that after iridectomy, there is yet much work to do, even if the pressure has improved. Figure 5–5 diagrams the important, but often neglected, management of primary angle closure following iridectomy.

What Are Some Useful Guidelines for Laser Iridectomy Technique?

Pretreatment

1. If the pupil is not already miotic from medications used to break an acute attack, constrict the pupil for a taut iris and easy penetration, for example, with pilocarpine 2 to 4% every 5 minutes for three doses until the pupil is nonreactive.
2. An alpha agonist such as brimonidine 0.2% (Alphagan) or apraclonidine 0.5 or 1.0% (Iopidine), and/or other glaucoma medications are helpful in minimizing the risk of a postlaser pressure spike.[42]

Technique

1. The Abraham or Wise iridectomy lenses greatly facilitate iris penetration.
2. Argon laser: Iridectomy with the argon laser is an art form.[43–47] Unlike the neodymium:yttrium-aluminum-garnet (Nd:YAG) photodisruptive iridectomy, this photocoagulative technique must be varied depending on differences in iris color and its relative tendencies to absorb or reflect laser energy. For example, "chipping away" with many high power/short exposure burns is very effective for dark brown irises. On the other hand, the "gas bubble" technique described by Hoskins and Migliazzo[46] is wonderful for light blue irises. For iris coloration in between these two extremes, a variety of techniques can be used such as the Simmons-Deppermann "drumhead" technique.[47] These methods are listed in Table 5–7; however, numerous techniques have been used successfully. This list may serve as a starting point from which surgeons can refine their own techniques.
3. Nd:YAG laser: The action of Nd:YAG photodisruptors, unlike argon laser photocoagulators, is independent of the propensity of the iris to absorb or reflect laser energy.[48,49] With the Nd:YAG laser, the same iridectomy technique can be used regardless of iris color. However, thin, light blue irises are more easily penetrated with Nd:YAG laser than thick, dark brown ones.
4. Site of iridectomy:

    - Base of iris crypt or thin spot
    - Iris freckle, if argon laser used
    - Avoid visible blood vessels, especially with Nd:YAG

- Peripheral site, especially if Nd:YAG used, to avoid damage to the underlying crystalline lens.
- Use the 2 or 10 o'clock position, so that the iridectomy is under the upper lid, but not the 12 o'clock position, where gas bubbles formed during the procedure can obscure visualization and interfere with completion of the laser procedure. Also, avoid creation of an iridectomy in the interpalpebral fissure (3 or 9 o'clock position) where postlaser visual symptoms and inadvertent laser damage to the macula are more likely.[50]
- If the procedure is going well and a second iridectomy can be made easily, some surgeons elect to perform a second iridectomy in case the first one becomes occluded later. This delayed closure is an unusual occurrence following Nd:YAG iridectomy for primary angle closure. Delayed closure is a more common problem following argon laser iridectomy, but can even occur after Nd:YAG iridectomy, especially for certain secondary angle closures such as neovascular glaucoma, uveitic glaucoma, or aphakic/pseudophakic pupillary block.

What General Guidelines Are Useful in Nd:YAG Laser Iridectomy?

The Nd:YAG laser is useful for initial laser iridectomy and particularly for completion of unsuccessful attempts at argon laser iridectomy. One should choose a site of thin iris as far in the periphery as clear visibility permits. In the periphery of the iris, damage to the underlying crystalline lens is least likely. Precise focusing is crucial to successful Nd:YAG iridectomy, so areas of arcus senilis should be avoided, as well as visible iris blood vessels to minimize hyphema during and after the procedure. Usually, one to five single shots of 4 to 7 mJ

Table 5–7. Argon Laser Iridectomy Techniques

"Gas bubble" technique for light blue irises (Hoskins and Migliazzo[46])

1. Create a 1.5-mm gas bubble on the surface of the iris with 1500 mW, 50 µm, 0.2–0.5 second burn (hold down the foot pedal until the desired bubble forms)
2. Immediately apply one or two additional shots, as needed, focused on the apex of the bubble; the gas bubble's inner surface will re-reflect laser energy toward the iris; this will usually achieve penetration, as evidenced by a plume of brown iris pigment carried by aqueous from the posterior chamber into the anterior chamber
3. Lower laser settings to 500–1000 mW, 50 µm, 0.05 seconds, and use multiple shots to enlarge and "clean up" the iridectomy

Modified "chipping away" technique for dark brown irises

In these eyes the areas of laser application tend to fill in with surrounding iris tissue after each shot, much like trying to dig a hole in dry sand; use many high-power, short-exposure burns: 1500 mW, 50 µm, 0.02–0.05 seconds

"Drumhead" technique for intermediate iris colors (Simmons and Deppermann[47])

1. Tighten the proposed iridectomy site like a drumhead by surrounding it with four "stretch" burns: 100–200 mW, 200 µm, 0.2 seconds
2. Penetrate iris with 500 mW, 50 µm, 0.5 second burns
3. "Clean up" site with 500 mW, 50 µm, 0.05 second burns

each are required. Some surgeons prefer to use the Nd:YAG burst mode for iridectomy. However, because with most instruments the procedure can be completed with single shots, many avoid the use of the burst mode, just in case it might increase the chance of damaging the underlying crystalline lens.

Active bleeding from the iris is common during Nd:YAG iridectomy, and may interfere with completion of the laser procedure. It can be temporarily controlled with the intermittent application of firm pressure upon the eye with the hand-held laser contact lens. Some surgeons minimize iris bleeding by pretreating the iridectomy site with argon laser photocoagulation.[51,52] A typical method used for such pretreatment is to tighten the desired site in similar fashion to the "drumhead" iridectomy technique, by surrounding it with four spaced burns of approximately 200 mW, 200 μm, and 0.2 seconds and then coagulating the central area with 10 to 20 burns of 400 to 800 mW, 100 μm, and 0.1 seconds.[47] The applications should be sufficient to tighten the iridectomy site without causing excessive pigment disruption. However, bleeding from the Nd:YAG iridectomy site very rarely causes significant problems.

It is not necessary to enlarge a small Nd:YAG iridectomy after penetration. Nd:YAG iridectomies tend to be smaller but "cleaner" than those made with the argon laser and are less prone to subsequent closure. Also, damage to the underlying lens capsule is more likely if additional photodisruption is used once a patent iridectomy has been achieved.

What Should Be Done After Laser Iridectomy?

The very important evaluation and management of the eye following iridectomy, as diagrammed in Figure 5–5, is seldom discussed and is often neglected. After laser iridectomy has relieved pupillary block, it is crucial to reexamine the eye and repeat the gonioscopy. The IOP may be improved following iridectomy, but there is much work yet to do. One-fourth of these eyes will require further treatment for glaucoma at some time in the future. In addition, 40 to 80% of fellow eyes of eyes with acute angle-closure glaucoma will have an acute attack within 5 to 10 years if they are not treated with prophylactic iridectomy. The pain and emotional upset resulting from an acute angle-closure attack in the first eye may increase sympathetic flow, induce pupillary mydriasis, and increase relative pupillary block, precipitating an acute attack of angle closure in the fellow eye during treatment of the first eye. Prophylaxis with 0.5 to 1% pilocarpine in the fellow eye is used by some, but it is not foolproof and, in some cases, can increase relative pupillary block and angle closure/closability. Prompt laser iridectomy in the fellow eye, if its angle is closed/closable, is necessary.[53,54] If the angle closure is truly unilateral, one should consider the differential diagnosis of secondary angle closure in the first eye, as listed in Table 5–1.

What If, Following Iridectomy, the IOP Is Down and the Angle Is Open and Not Closable?

Proceed with laser iridectomy to relieve relative pupillary block in the fellow eye if its angle is closable as shown in Figure 5–5.

Caution: Just because the IOP is improved following iridectomy and the angle is open, do not assume that the iridectomy is patent, especially if the argon laser has been used. The pupillary block may have been relieved by peaking of the pupil due to shrinkage of iris tissue from argon laser applications, even if penetration of the iris is incomplete. This pupilloplasty effect is usually transient, so be certain of a patent iridectomy to avoid recurrence of relative pupillary block and angle closure. Conversely, a permanent spontaneous "cure" of pupillary block-induced angle closure can occur due to a sector of stromal iris atrophy resulting from the ischemia of an acute attack that alters the lens/iris interface, thereby permanently relieving relative pupillary block.

What If, After Iridectomy, the IOP Remains Elevated with Fresh Peripheral Anterior Synechiae Following Medical Therapy and Laser Iridectomy for Acute Angle Closure?

Fresh peripheral anterior synechiae can occasionally be broken with laser peripheral iris gonioplasty and/or operative goniosynechialysis. Gonioplasty creates surface iris burns to shrink and flatten the iris tissue and pull it away from the trabecular meshwork.[23] Operative goniosynechialysis has been reported to break fresh synechiae and improve facility of outflow up to 1 year following an acute attack of primary angle closure.[21,22]

What If, After Iridectomy, the Angle Remains Closed/Closable from Plateau Iris Syndrome?

With plateau iris syndrome the angle is still appositionally closed/closable after iridectomy, which eliminates relative pupillary block but not the plateau iris mechanism. Remember that most cases of angle closure with plateau iris configuration, as seen gonioscopically prior to iridectomy, are actually due to increased relative pupillary block, which is cured by iridectomy. To resolve plateau iris syndrome, where angle closability persists after iridectomy, one must flatten the peripheral iris to remove it from the proximity of the trabecular meshwork with chronic miotic therapy or laser peripheral iris gonioplasty.

Chronic Miotic Therapy for Plateau Iris Syndrome

Chronic miotics were the only available therapy for the prevention of progressive synechia formation in plateau iris syndrome prior to the introduction of argon laser gonioplasty. Chronic miotic therapy, such as pilocarpine 0.5 to 1% every 12 hours, is much less convenient, less well tolerated, and less dependable than laser gonioplasty, however. Dapiprazole (Rev Eyes), which achieves miosis by α-adrenergic blockade, may offer an alternative, but at this time it is costly and has a relatively short shelf life following its reconstitution.

Laser Peripheral Iris Gonioplasty for Plateau Iris Syndrome

Laser peripheral iris gonioplasty, as outlined in Table 5–6, is the preferred method of relieving the plateau iris mechanism.[55,56] With this technique, argon laser burns are applied to the peripheral iris roll to shrink and pull it away from the angle. The effect is often transient, and retreatment is often necessary. Therefore, it is imperative that these eyes are followed indefinitely with periodic gonioscopy.

Remember that plateau iris syndrome may develop years after iridectomy, so periodic gonioscopy should be performed on all patients who have had iridectomy for primary angle closure.

What If, After Iridectomy, the IOP Remains Elevated Without Fresh Peripheral Anterior Synechiae and In the Absence of Plateau Iris Syndrome?

In this situation, one should proceed to medical therapy, laser trabeculoplasty, and filtration surgery, as needed for control of IOP of this open angle component of the patient's "mixed mechanism" glaucoma.

Treat IOP with medical glaucoma therapy just as with chronic open angle glaucoma. If medical therapy is unsuccessful, consider laser trabeculoplasty, depending on the desired and existing IOP, the extent of optic nerve and visual field damage, and the fraction of the circumference of trabecular meshwork available for trabeculoplasty. For example, if the pressure is 26, the desired pressure is 18, and 11 clock hours of trabecular meshwork are available for trabeculoplasty, then it is a reasonable option. On the other hand, if the pressure is 45, the desired pressure is 16, and only 2 clock hours of meshwork are visible, then laser is a waste of time and may pose a hazard. In actual practice, most cases lie in between these two extremes and the surgeon must exercise his or her judgment as to the value of laser trabeculoplasty in the particular setting. As a general rule, potentially dangerous posttrabeculoplasty IOP elevation should be minimized by treating no more than half of the visible trabecular meshwork at a single laser session.

If medications and laser trabeculoplasty fail to control the IOP, filtration surgery is necessary.

What Particular Problems Does Filtration Surgery Pose in These Eyes?

Glaucoma filtration operations in eyes with primary angle closure can be exceedingly challenging and fraught with unique problems. In the characteristically small, hyperopic and deep-set eyes with primary angle closure, surgical exposure is usually far less than optimal. If the eye has recently had an acute attack of angle closure, visibility of anterior segment anatomy is often decreased by the presence of corneal edema. Also, conjunctival hyperemia predisposes to intraoperative bleeding, further compromising visibility. This is

complicated by a small anterior segment in which to maneuver. In addition to these technical problems, there is an increased risk of intraoperative suprachoroidal hemorrhage and of postoperative malignant (ciliary block) glaucoma.

Future Considerations

The treatment of glaucoma in general, and therefore that of primary angle-closure glaucoma, will evolve and improve. As more glaucoma drugs have emerged, expanding the medical therapeutic options, the fraction of patients unable to use medications because of expense, inconvenience, and side effects has decreased. In particular, the continued development of aqueous suppressant medications increase the options for the ophthalmologist to lower the intraocular pressure even in the face of synechial angle closure. As the understanding of neuroprotectve medications grows, patients with primary angle closure, just like those with other forms of glaucoma, will benefit from medications that enhance the optic nerve's ability to resist pressure-induced damage.

Through the years, instrumentation and techniques for laser iridectomy have continued to improve. Although Nd:YAG laser iridectomy is, at present, a wonderful procedure for patient and physician, iridectomy technology will doubtless become even better.

Relative pupillary block and the beneficial effect of laser iridectomy are very well understood. In contrast, plateau iris syndrome, despite recent progress, remains an enigma. A better understanding of the mechanics of plateau iris will yield a wider and more efficacious array of therapeutic options than laser gonioplasty and chronic miotics.

Finally, and perhaps most important, a better understanding and wider appreciation of the demographics of primary angle closure will increase awareness of the problem and lead to earlier detection, before permanent synechial angle closure and optic nerve damage occur.

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◆ 6 ◆

Glaucoma Associated with Raised Episcleral Venous Pressure: The "Red Eye" Glaucomas

Kenneth W. Olander

Definition

How Is Glaucoma from Raised Episcleral Venous Pressure (EVP) Defined?

Increased EVP causing glaucoma may be seen in at least 17 clinical situations (Table 6–1). It is a type of secondary open-angle glaucoma and has four subtypes: (1) obstruction of venous drainage, (2) arteriovenous fistula, (3) ocular episcleral venous anomalies, and (4) idiopathic. This glaucoma is not rare and is commonly underdiagnosed, especially the idiopathic form and those caused by subclinical dural shunts.

Table 6–1. Classification of Elevated Episcleral Venous Pressure (EVP)

I. Venous obstruction
1. Retrobulbar tumors
2. Thyroid ophthalmopathy
3. Superior vena cava syndrome
4. Congestive heart failure
5. Thrombosis of cavernous sinus or orbital vein
6. Vasculitis of the episcleral and/or orbital vein
7. Jugular venous obstruction
8. Inversion therapy

II. Arteriovenous anomalies
9. Carotid-cavernous sinus fistula
10. Orbital varix

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Table 6–1 Continued

	11. Sturge-Weber syndrome
	12. Orbital meningeal shunts (dural shunt syndrome)
	13. Carotid jugular venous shunts
	14. Orbital vascular shunts
III.	**Idiopathic causes**
	15. Sporadic
	16. Familial
IV.	**Medications**
	17. Oral and topical

Modified from Ritch, Shields, and Krupin, 1996. By permission from C.V. Mosby.

Epidemiology and Importance

How Important and How Common Is Glaucoma from Raised EVP?

This is an important class of glaucoma because it may present at any time to anyone. The recognition of eyes with raised EVP is important for at least three reasons[1]:

1. The episcleral veins serve as collector channels for the outflow of aqueous from the eye via Schlemm's canal and the aqueous veins. Thus, a chronic elevation of pressure in the episcleral veins can result in the elevation of intraocular pressure (IOP) with resulting glaucoma and damage.
2. The occurrence of glaucoma secondary to raised EVP dictates that an extensive medical, neurologic, and radiologic evaluation be performed, including arteriography and venography, to determine the cause of the raised EVP.
3. Glaucoma secondary to raised EVP may not respond to some of the medical agents generally used in the treatment of other forms of open-angle glaucoma.

There is no single subspecialty that sees a lot of cases, as this type probably constitutes less than 1% of glaucomas. The patients typically have a red eye, but may not always notice it. Comprehensive ophthalmologists may be the first line of detection of this potentially fatal condition.[2] It is almost impossible to define the exact frequency of this disease. As a glaucoma specialist, I had four cases over a 4-year period and then none for many subsequent years. Cornea specialists may see these cases of red eyes and may pick up the elevated IOPs. Neurophthalmologists may see some cases presenting with neurologic defects. Orbital specialists may see patients with pulsating exophthalmos.

A review of the literature indicates a wide range of presenting cases. Keltner et al[3] saw 18 cases over 9 years, or two per year. Hieshima et al[2] saw 131 cases over 12 years, or 11 per year. Regardless of how many cases are seen, treatment is often challenging and typical medical means do not work. Appropriately diagnosing and treating the underlying cause frequently cures this glaucoma, but often surgical intervention is required.

Diagnosis and Differential Diagnosis

What Is the Normal Drainage of Aqueous Out of the Eye?

It is necessary to review some basic scientific principles regarding the drainage of aqueous out of the eye and how the vascular plexus and venous pressure cause glaucoma. According to Weinreb and Karwatowski,[4] it was Sidel in 1923 who was the first to inject ink into the anterior chamber and observe its appearance in the episcleral veins. They also point out that it was not until 1942 that Ascher observed clear aqueous humor laminated with blood in a vessel demonstrating an anatomic connection between Schlemm's canal and the episcleral veins. Recent scanning electron microscopy of vascular resin casts has added significantly to our detailed understanding of this anatomy.[5] It should be noted that this is a valveless system with frequent interconnections. Indeed, blood can be diverted from one system to the other, with flow in any direction, depending on the hydrostatic pressure gradient.

There is a constant flow of aqueous humor through the anterior segment of the eye. We know that the aqueous is formed by the ciliary processes, passes through the pupil, and exits in the angle. Most of the fluid enters the venous system by way of the trabecular meshwork and Schlemm's canal; this is called convention outflow. A smaller amount of aqueous passes through the ciliary muscle and the iris to reach the superciliary and superchoroidal spaces. From there, the fluid passes through the sclera or through the loose connective tissue around the penetrating nerves and vessels. This is called unconventional outflow.

What Is Conventional Outflow?

The episcleral tissue is a loose connective and elastic tissue covering the sclera and connecting to the conjunctiva. It is continuous with the loose tissue of Tenon's space and tightly connects to denser sclera in its deeper layers. It contains multiple blood vessels. Behind the ocular attachments of the recti, the episcleral tissue is thin and the vessels, two veins to each artery, form a wide meshed net. The arteries here come from the posterior ciliary network. In front of the attachment of the muscles, the episclera is much thicker and much richer in vessels. The meshes of the vascular net are smaller. A capillary net exists only in this anterior zone on the sclera. When there is a marked filling of this net, it is called ciliary injection. Aqueous humor drains through the trabecular meshwork into Schlemm's canal. Arising from the outer circumference of the canal are the external collector channels that drain into the episcleral and conjunctival venous plexus. There are 25 to 35 collector channels. When one of the connects directly with a surface vein, it can be seen on slit-lamp examination and is termed an "aqueous vein." Some 14 or more branches from the ciliary muscle also traverse the sclera to join the plexus of veins adjacent to the canal. Aqueous veins of Ascher vary in size from 0.01 to 0.1 mm in diameter. They are found near the limbus and most often inferonasally commencing in a hook-shaped bend where they come out of the sclera. They contain a clear fluid, and a laminated flow of blood and clear fluid can often be seen.[6] Thus, to summarize, the aqueous drains from Schlemm's canal into a deep scleral plexus of veins, and then via the intrascleral plexus to the episcleral plexus and the subconjunctival plexus at the limbus. In addition, from direct connections, aque-

ous veins pass from the deep sclera to the episcleral plexus. Under conditions of increased episcleral venous pressure, the flow will be reversed and blood is frequently seen in Schlemm's canal with simple gonioscopy.[7]

What Affects the Aqueous Humor Dynamics?

In the steady state, the dependence of IOP on EVP is approximated by the modified Goldmann equation $Po = f/c + Pev$, where *Po* is the IOP, *Pev* is the EVP, *f* is the aqueous inflow, and *c* is the outflow facility. This equation states that for every 1 mm increase in EVP, there is a concomitant increase of 1 mm in IOP. Numerous studies have been done to test this hypothesis. In 1968, the validity of the Goldmann equation was first tested in humans.[8] It was observed that for every millimeter of mercury increase in EVP, there was only a 0.75-mm increase in ocular pressure. The term *pseudofacility* is used to describe the decrease in inflow, secondary to an increase in IOP, and is frequently a part of a trick question given to ophthalmology residents, as follows: "What is the tonographic outflow facility in a patient with elevated IOP due to increased EVP?" There is a natural tendency to answer that the outflow facility is abnormal because, obviously, the IOP is elevated. This would be incorrect. The tonographic outflow facility, at least in the disease process, can be and usually is normal despite the elevated IOP. This phenomenon has been studied in normal volunteers using a blood pressure cuff placed around the patient's neck. When it is inflated, the episcleral venous pressure becomes elevated, but the IOP increases to a slightly smaller degree. This effect is small and the overall phenomenon indicates that the aqueous humor formation does not self-regulate in response to the level of IOP.[9] There are no known feedback loops or anatomic connections that would allow such a regulatory process to occur. It is tempting to speculate that a chronically elevated EVP could be an important factor in all chronic open-angle glaucoma, but this has not been demonstrated to be the case.[10] However, for secondary types of open-angle glaucoma, episcleral venous pressure is important (Table 6–2).

Table 6–2. Ocular Findings Suggestive of Raised Episcleral Venous Pressure (EVP)

Slit-lamp exam for "red eye"; blood in aqueous veins
Gonioscopy showing blood in Schlemm's canal
Dilated fundus exam showing distension of retinal veins
Extraocular motility exam showing duction deficiencies
Arteriovenous fistula (AVF) screening tests showing neurologic cuts
Orbital exam showing bruit, vascular anomalies, or traumatic scars
Tonography sometimes helpful
Presence of exophthalmos—stable or pulsatile
Increased cup-to-disc ratio showing chronically increased IOP
EVP measurement directly elevated
Ophthalmodynamometry showing arteriovenous malformations
Orbital ultrasound showing soft tissue masses—may increase with position changes

What Is Uveoscleral or Unconventional Outflow?

Bill[11] was among the first to point out that flow through the trabecular meshwork and Schlemm's canal seems to involve a well-designed fluid transport system. In contrast, uveoscleral flow seems more primitive and resembles a leak more than a well-designed fluid transport system.[7] The aqueous humor enters the ciliary muscle fibrils through the uveotrabecular meshwork, the ciliary body space, and the root of the iris. Fluid passes between the bundles of the muscle until it reaches the supraciliary and suprachoroidal spaces. The aqueous humor leaves the eye through the spaces around the penetrating nerves and blood vessels and through the sclera. Even large molecules, such as horseradish peroxidase, can pass through intact sclera. Uveoscleral flow seems to be present in most species, but the amount of aqueous humor transported by the system varies considerably, being approximately 3% in rabbits and 50% in some species of monkey; in humans it is estimated that 5 to 25% of the total outflow is through this unconventional pathway. Direct measurement of uveoscleral flow is very limited, and the human eyes that have been studied may be atypical. Also, outflow increases up to fourfold when the anterior segment is inflamed. It appears that uveoscleral flow increases when the IOP is raised from atmospheric pressure to the level of the EVP; however, above this pressure level, uveoscleral flow is largely independent of IOP. The main resistance to uveoscleral flow is the tone of the ciliary muscles. Factors that contract the ciliary muscles, such as pilocarpine, lower the flow, whereas drugs that relax the ciliary muscles, such as atropine, increase the flow. The prostaglandins significantly increase uveoscleral outflow, and the effects of a prostaglandin/pilocarpine combination are largely unstudied. A few studies indicate that epinephrine may lower IOP by increasing uveoscleral outflow. Cyclodialysis is an older operation designed to lower IOP by detaching a portion of the ciliary body from the scleral spur. There is evidence that this acts to increase uveoscleral outflow.[7]

What Is the Normal Venous Drainage of the Orbit?

The main venous supply from the orbit is provided by the superior ophthalmic vein, the inferior ophthalmic vein, and the central retinal vein (Fig. 6– 1).[12] The supply to the eyelids is supplemented by branches of the superficial temporal and facial veins. These vessels have no valves, are markedly tortuous, and display many plexiform anastomoses. They communicate with the veins of the face, with the pterygoid plexus, and with the veins of the nose. They ultimately drain into the cavernous sinus.

The superior ophthalmic vein is formed near the root of the nose via communication from the angular vein and the supraorbital vein. It passes into the orbit above the medial palpebral ligament and then accompanies the ophthalmic artery across the optic nerve and under the superior rectus to the superior orbital fissure, where it is usually joined by the inferior ophthalmic vein. It then leaves the orbit to enter the cavernous sinus. The inferior ophthalmic vein forms as a venous plexus on the orbital floor. It takes branches from the lower lid, tear sac, inferior rectus, oblique muscles, and the two inferior vortex veins. The blood flow passes posteriorly, forming two veins, getting into the medial compartment of the supraorbital fissure, and then into the cavernous sinus. A lower branch may pass through the intraorbital fissure to the pterygoid plexus.

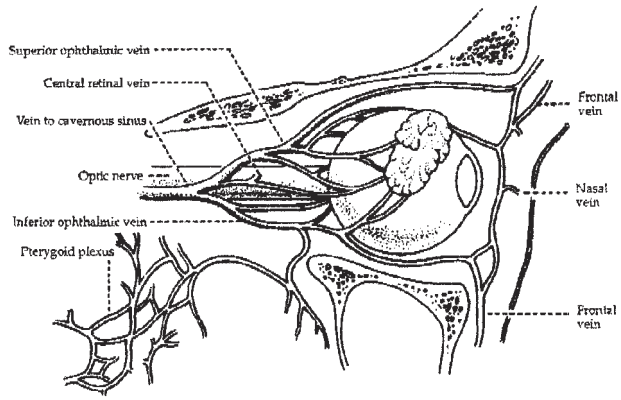

Figure 6–1. Venous drainage of the orbit. Superior ophthalmic vein, inferior ophthalmic vein and facial veins are the three principal routes of orbital venous drainage. (From Ritch, Shields, and Krupin, 1999. By permission from C.V. Mosby.)

The central retinal vein is a confluence of all of the branches of the retinal venous circulation. The upper veins form a superior papillary vein and the lower and inferior papillary vein, which unite in the region of the optic cup. About 10 mm behind the globe, the central retinal vein turns downward at a right angle to leave the optic nerve. It usually passes through the sheath of the optic nerve and emerges behind the artery, where it runs posteriorly and passes through the oculomotor foramen to enter the cavernous sinus directly. The cavernous sinus drains primarily through the superoinferior petrosal sinuses into the internal jugular vein. A small amount drains through the external jugular veins, and still less through the suboccipital plexus into the vertebral and deep cervical veins. The cavernous sinus also has connections with the ipsilateral pterygoid plexus and the contralateral cavernous sinus. Facial veins communicate with the superior ophthalmic vein through the nasal, frontal, and lacrimal eyelid veins and communicate with the inferior ophthalmic vein through the infraorbital vein. The facial veins drain mainly into the external jugular veins.[4,6]

How Is the EVP Measured?

The episcleral vessels can easily be differentiated from the conjunctival vessels by the relative mobility of the latter when they are in touch with the tip of a pressure chamber (Table 6–3). The episcleral veins are differentiated from the anterior ciliary arteries by the narrower caliber, straighter course, and slightly darker color of the veins. Glaucomatous damage develops in certain patients because of elevated EVP. For an instrument to be practical in the clinical environment, it should be easily operated by one observer, require little calibration, be of compact size, permit stereopsis before and during the measurement, and provide good reproducibility. Such an instrument, called a venomanometer, has been developed by Zeimer and associates.[13] Basically, the instrument is mounted directly on the slit lamp. It looks similar to an applanation tonometer. There is a flexible transparent tip of molded silicone rubber covering an air-sealed piston.

Table 6–3. Medical Evaluation of Patients with Increased Episcleral Venous Pressure (EVP)

Blood test for thyroid disease
Look for exophthalmos—stable or pulsatile
Listen for bruit in orbit or neck
Do x-ray/computed tomography (CT) scan of skull, orbit, foramen
Do electroencephalogram (EEG)
Examine carefully for skin lesions suggestive of congenital vascular disease or scars indicating trauma
Performing systemic measurement of venous pressure in arms
Get a complete neurologic examination
Order selective external and internal carotid arteriogram
Order orbital venogram
Consider digital subtraction angiogram or color Doppler ultrasound

There is a rotating dial that controls the position of the air-sealed piston. The position of the piston determines the volume of air in the chamber and therefore its pressure. The instrument is available currently for approximately $850 according to personal communications with Peter Netland, M.D., Ph.D.

The EVPs in normal eyes and in eyes with open-angle glaucoma have not been shown to be significantly different. However, Kupfer[10] and Talusan and Schwartz[14] have reported that ocular hypertensive eyes have a slightly lower EVP than normal eyes. There are some problems in measuring the EVP. Most of these problems are of an anatomic nature. Different observers may select different blood vessels, which may yield slightly different readings. Also, the selection of the end-point indication of increased EVP is somewhat arbitrary. Tissue compressibility has been reported to be negligible, and the pressure required to blanch the vessel to the one-half point accurately reflects the intraluminal pressure. No evidence has been found for regional differences in EVP within the quadrant of an eye or between the two eyes. There is a significant correlation of EVP with age. The normal EVP runs 7.6 ± 1.3 mm Hg. When the EVP is raised by some disease process, the IOP is usually increased as well; however, the relationship between the pressure increases is more complex in the chronic situation than in the acute, experimental situation. Many conditions, for example carotid cavernous fistula, that increase EVP also cause ocular ischemia, and that reduces the aqueous humor formation and IOP. Also, acute elevations of EVP increase the facility of outflow, whereas chronic elevations of pressure may produce secondary changes in the angle structures, and ultimately decrease the outflow facility.

What Clinical Conditions Cause Raised EVP?

Various clinical conditions may result in elevated EVP. As discussed below, patients may present with a multitude of ocular and/or systemic signs and symptoms. The steps in an evaluation include a history; measurement of visual acuity, IOP, and EVP; slit-lamp examination; neurophthalmic examination, gonioscopy; and fundus examination. Figure 6–2 delineates various steps that may help in the diagnosis.

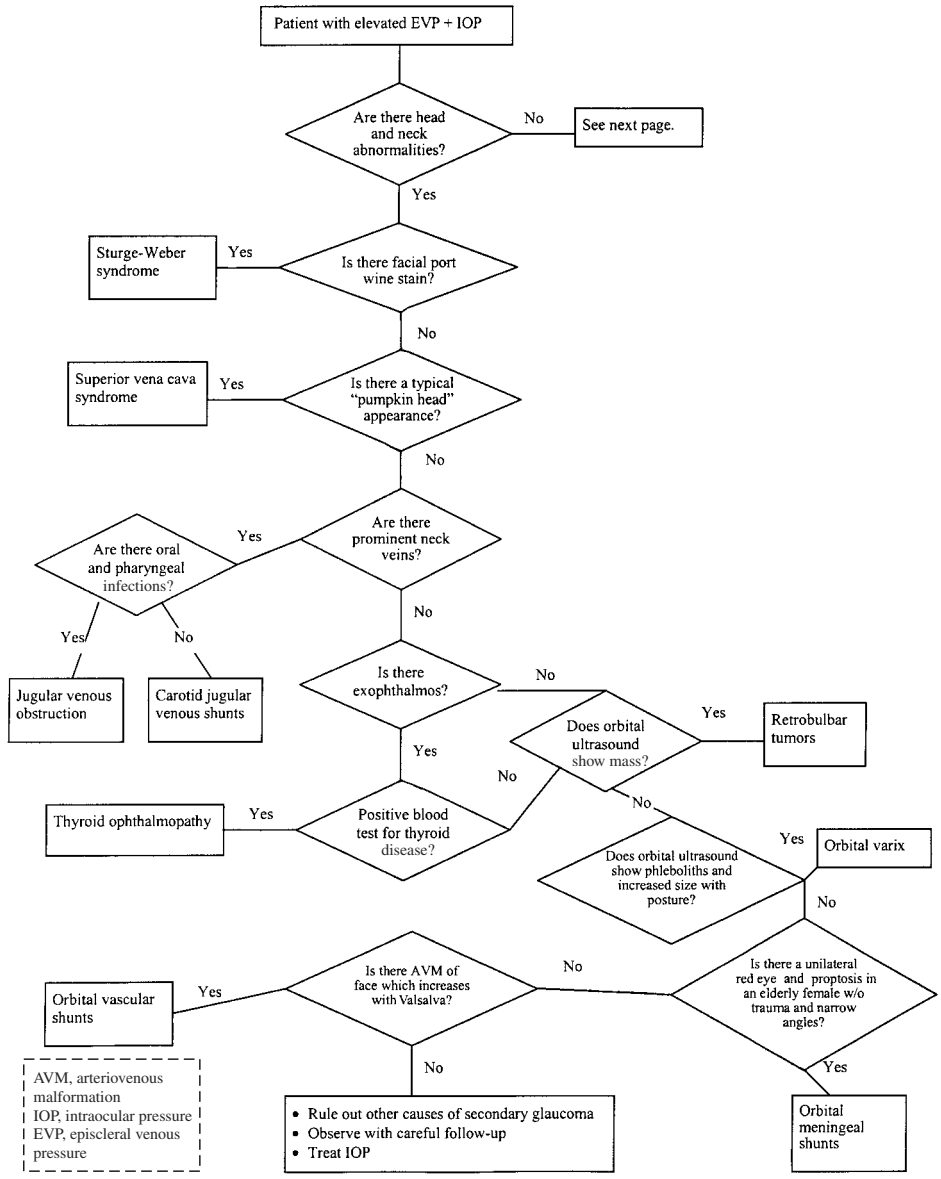

Figure 6–2. Algorithm for diagnosing causes of increased EVP.

What Venous Obstruction Problems Cause Raised EVP?

Orbital venous abnormalities and lymphangiomas have been generally classified on morphologic grounds; however, this has led to a confusing scientific dialogue. The members of the Orbital Society have recently issued a statement classifying orbital vascular malformations based on their hemodynamic relationships (Table 6–4). Orbital vascular malformations fall into three categories: no flow, venous flow, and arterial flow. Assignment to each group is based on pertinent clinical and imaging criteria. Mixed forms with both no flow and venous components are grouped with the venous flow category.[15]

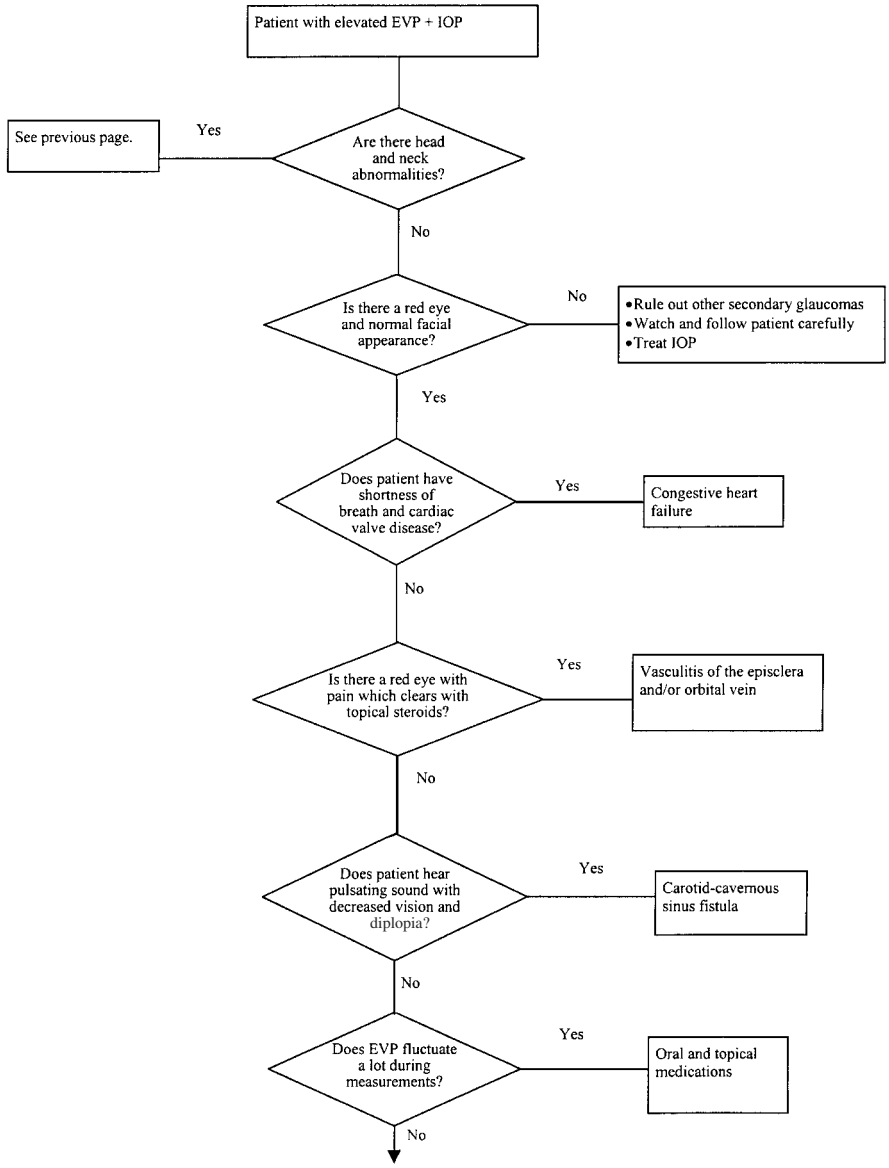

Figure 6–2. Continued. (*Figure continued next page.*)

Do Retrobulbar Tumors Cause Glaucoma?

Any orbital tumor that compresses the venous system may result in glaucoma secondary to backup in venous system drainage apparatus. Nordman et al reported 14 cases caused by a variety of tumors in 1961 (translation cited by Weinreb and Karwatowski[4]). This condition would generally be diagnosed with a computed tomography (CT) scan or an ultrasound. Intraocular tumors, such as ciliary body melanomas, may present with engorgement of the episcleral veins, which are called the "sentinel vessels." However, these engorged

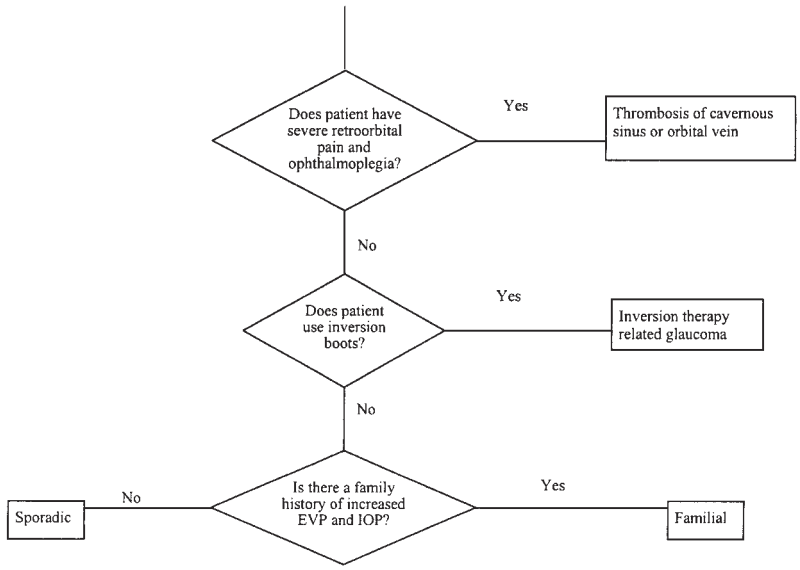

Figure 6–2. Continued.

vessels are localized over the tumor site and are restricted to a single quadrant, and glaucoma is not commonly seen.

Does Thyroid Ophthalmopathy Cause Glaucoma?

Thyroid eye disease is known by a variety of names, and the hormonal defect of this condition is unclear. Patients can be hypothyroid, euthyroid, or hyperthyroid when the problems begin. The physical findings are variable, and include exophthalmos, chemosis, and dilated conjunctival and episcleral vessels. Histopathologically, there is infiltration of the orbit including rectus muscles with lymphocytes, mast cells, and plasma cells. IOP can be increased for

Table 6–4. Proposed Classification of Orbital Vascular Malformations

No flow malformations
Hemodynamically isolated
Applicable to so-called lymphangiomas
Venous flow malformations
Applicable to so-called primary varices
Including distensible and nondistensible varieties
Including mixed forms with venous and no flow components (grouped here to emphasize the clinical importance of the venous relationship)
Arterial flow malformations
Arteriovenous malformations or arterialized veins distal to them
Applicable to so-called secondary varices

From Harris GJ: Orbital vascular malformations: a consensus statement on terminology and its clinical implications. Am J Ophthalmol 1999; 127:453–455. By permission from Elsevier Science.

several reasons, including elevated EVP. Elevated EVP may result from the retrobulbar infiltration process.[16] Jorgenson and Guthoff[16] reported that 5 of 35 patients with endocrine orbitopathy had increased IOP in primary gaze. EVP was high, being between 16 and 23 mm Hg. It was speculated that compression of the ophthalmic veins by swollen extraocular muscles resulted in abnormal EVP and subsequently raised IOP. Also, the contraction of extraocular muscles resulted in the abnormal EVP and subsequently raised IOP. Also, the contraction of extraocular muscles may cause abnormally high IOPs in some specific directions of gaze. Usually fibrosis of the inferior rectus muscle significantly increases IOP in upgaze.[4] The presence of exophthalmos with abnormal blood tests and either orbital ultrasound or CT scan of the orbit showing enlarged extraocular muscles will aid in the diagnosis of this condition.

Does Superior Vena Cava Syndrome (SVCS) Cause Glaucoma?

Obstruction of the superior vena cava will result in increased venous pressure in those areas in which it provides venous drainage. These patients show edema and cyanosis of the face and neck as well as dilated vessels in the head, neck, chest, and upper extremities. Obstruction may increase the intracranial pressure, causing headaches, stupor, vertigo, seizures, and mental changes. Ocular findings include exophthalmos, papilledema, and prominent blood vessels in the conjunctiva, episclera, and retina.[17] The IOP is usually elevated and is greater when the patient is in the supine position. It has been reported that glaucomatous cupping occurs infrequently with this syndrome, despite the elevated IOP. Some researchers propose that cupping does not occur because the IOP is counterbalanced by elevated intracranial pressure.[17] Before the advent of antibiotics, this syndrome was commonly caused by mediastenitis secondary to the pulmonary infections of syphilis or tuberculosis. Presently, malignancy is the cause of 97% of these cases. Occasionally, aortic aneurysm, enlarged hilar nodes, and intrathoracic thyroid disease may be involved. Diagnosis is suggested by the clinical appearance of the face and neck, "pumpkin head" appearance, and by altered neurologic status accompanied by frequent complaints of headaches. The glaucoma is bilateral and usually gives rise to no subjective complaints. The site of obstruction may be demonstrated by venography or scintigraphy, but not without attendant hazards. These tests are generally not warranted. SVCS is usually more frequent on the right side, with a ratio of 4:1, and at present the most common cause is bronchogenic carcinoma.[18]

Does Congestive Heart Failure Lead to Glaucoma?

A report in the German-language literature by Bettelheim[19] has demonstrated that elevated EVP in pulmonary hypertension can cause glaucoma and it was termed "cardiogenesis glaucoma." No details are available, as the original article has not been translated into English. Nevertheless, this type of glaucoma points out that many case reports in the literature present intriguing diagnostic questions that remain unanswered. Another cardiac abnormality causing bilateral corkscrew episcleral veins occurred in a 56-year-old woman with an insidious onset of redness in both eyes, developing over a course of 6 months.[20] She

had a history of rheumatic heart disease and had marked tricuspid valve incompetence. She did not have elevation of her IOP. The important concept in this article concerns the use of orbital color Doppler ultrasound to detect this unusual episodic biphasic blood flow present in both superior ophthalmic veins. Similar Doppler flow patterns were demonstrated on both of this patient's internal jugular veins. Even though the patient was not in congestive heart failure at the time of her exam, it appears that the congestive effect in this patient was caused by tricuspid incompetence transmitting the ventricular pressure as reversed flow in the superior ophthalmic veins. Nevertheless, it was not a constant arterialized reversal of flow seen in a typical carotid cavernous sinus fistula. The noninvasive nature of color Doppler imaging and its ability to perform in an outpatient clinic makes it a choice over standard angiography in many situations.

Does Thrombosis of the Cavernous Sinus or Superior Ophthalmic Vein Cause Glaucoma?

Occlusion or thrombosis of the superior ophthalmic vein or the cavernous sinus is a nonspecific finding that may be caused by such disorders as tumors of the skull base or nasopharynx. Sometimes no cause can be found. Brismar and Brismar[21] described eight cases with increased EVP and glaucoma. Typically, these patients will have third, fourth, and sixth cranial nerve palsies. Retroorbital pain associated with ophthalmoplegia is typical, and more serious underlying causes need to be ruled out. Septic cavernous sinus thrombosis is not difficult to distinguish because of its fulminant nature. Many of these cases show spontaneous remission. Improvement with steroid therapy does not help in establishing the etiologic cause. Extensive clinical and radiologic evaluation should be done on these patients to discern a more serious underlying disorder. These tests would include carotid angiography, tomography of the skull base, and nasopharyngoscopy with blind biopsies. Orbital phlebography has a definite value in the diagnosis of these patients. Infrequently, it is quite a challenge to distinguish between Talosa-Hunt syndrome and aseptic cavernous sinus thrombosis. Although the IOP was normal in these eight cases, many of them had abnormalities of the optic nerve and visual field defects that had not been clearly described. Conjunctival venous dilations and retinal venous dilations were present in a number of these cases.

Does Vasculitis of the Episcleral and/or Orbital Veins Cause Glaucoma?

Patients with anterior scleritis may have elevated IOP related to raised EVP. In a German-language article by Jorgensen and Guthoff,[16] 64 patients were described with dilated vessels and glaucoma. Raised EVP was the cause of the elevated IOP. Jorgensen and Guthoff described cases of spontaneous carotid cavernous fistula, Sturge-Weber syndrome, orbital tumors, endocrine ophthalmopathy, anterior scleritis, and idiopathic cases. A variety of pathophysiologic mechanisms were involved. After systemic steroid therapy, both raised IOP and elevated EVP returned to normal.

Can Jugular Venous Obstruction Cause Glaucoma?

In 1946, Meyer[22] described a type of secondary glaucoma due to inflammatory jugular phlebostenosis and called it "glaucoma exogenicum." He traced clinically the cause of glaucoma to jugular phlebostenosis caused by proliferative endophlebitis. He claimed that the bulk of blood entering the head is drained off by the internal jugular veins on either side of the neck. A relatively small amount of venous blood passes through the external jugular veins, and another very small portion returns by way of the suboccipital plexus into vertebral and deep cervical veins and from there into the anominate veins. In Meyer's era the primary cause of the jugular endophlebitis could be traced to oral infections, such as acute tonsillitis, and other pharyngeal infections. Meyer found that the application of leeches in the treatment of purulent phlebitis in the lower extremities was beneficial, and he stated that previously ophthalmologists had used leeches in glaucoma cases. They applied leeches over the temporal region in glaucoma patients and this application resulted in a temporary decongestion of the eye. He claimed that "recalibration" of the jugular veins with leeches in inflammatory obstruction brings on a total decongestion of the whole head area and therefore has a permanent therapeutic effect.

Does Inversion Therapy Lead to Glaucoma?

The IOP typically increases as the body assumes a more dependent posture. When the body is totally inverted in a vertical orientation, the IOP rapidly rises to a level approximately double the normal erect posture. Eleven patients had their EVP and gonioscopy performed in the supine and inverted positions.[23] The IOP rose rapidly; within 10 seconds 70% of the increase had occurred and within 1 minute a constant value was reached. It was felt that the rapid rise in pressure was due to mechanical compression of the orbital contents against the globe, and that congestion and expansion of the uveal tissue from increased venous and arterial pressure within the orbit also played an important role. The investigators felt that the sustained increase in venous pressure in the orbit and additional contributions to the IOP may be due to a net increase in the rate of aqueous production. Alterations in the rate of uveoscleral outflow may also be a factor. They found that for every 0.83 mm Hg increase in EVP, there was a 1 mm Hg increase in IOP.

What Arteriovenous Anomalies May Lead to Glaucoma?

Various arteriovenous anomalies that may cause glaucoma are described below.

Does Carotid-Cavernous Sinus Fistula (CCSF) Cause Glaucoma?

CCSF can be subdivided into (1) etiologic (i.e., spontaneous or traumatic), (2) hemodynamic, (i.e., high or low flow), and (3) anatomic (i.e., direct or dural). CCSFs provide a free communication between the internal carotid artery and the surrounding cavernous sinus resulting in high blood flow and high mean pressure in the shunt.[3] A reversal of the blood flow in these vessels leads to conges-

tion of the orbital veins and soft tissue. Shunting of the blood may produce ocular ischemia, and there may be a pulsatile exophthalmos. Patients with CCSF often (75%) give a history of previous trauma. Many of these patients have a dramatic appearance with pulsatile exophthalmos, chemosis, lid edema, vascular engorgement, and restriction of ocular motility. The conjunctival episcleral veins have a tortuous corkscrew appearance. These findings usually occur on the same side as the fistula, but because of connections between the cavernous sinuses, the findings may be bilateral or alternating.[7] Occasionally, the clinical findings may mimic thyroid disease. Typically, the patient is a young man who presents soon after a severe head injury with the above findings. In cases of nontraumatic etiology, the patients are typically postmenopausal women. They generally have no bruit, their proptosis is minimal, and their eyes do not pulsate. Most commonly, patients present because of chronic red eye. The increased IOP in nearly every patient can be severe and may cause blindness.[24] These patients often complain of a noise in their ears, and a bruit is often present over the frontal or temporal regions or on the globe. The IOP is elevated because of the increased EVP, although angle closure and neovascular glaucoma have been reported.[25,26] Skull films, orbital ultrasonography, or CT or magnetic resonance imaging (MRI) scans confirm the diagnosis along with the initial clinical impression, but arteriography provides the most detailed information about these fistulas. Treatment can be difficult and is usually reserved for individuals who have severe pain, incapacitating bruit, progressive glaucomatous vision loss, or other serious complications.[27] A variety of embolization and balloon catheter techniques have been developed with increasing success, but there is still a fairly high morbidity and mortality.

Does Orbital Varix Cause Glaucoma?

Orbital varices are typically found in young persons who have a history of intermittent unilateral proptosis beginning in early childhood. The proptosis may be worsened by increasing the venous pressure in the head and neck such as found in the Valsalva maneuver or bending over. Patients present with dilated veins in the eyelid, anterior orbit, sometimes acute orbital hemorrhage, or thrombophlebitis. Approximately 50% of these patients will have other systemic venous abnormalities involving the scalp, palate, and forehead, and rarely it may be associated with Klippel-Trenaunay-Weber syndrome. The conjunctiva may show multiloculated cysts, which may be misdiagnosed as orbital lymphangioma. Orbital venography will show venous angioma composed of a network of large, dilated, and tortuous veins overlying the frontal bone draining into a dilated angular vein. In a typical patient, as reported by Rathburn et al[28] in 1970, the dye flowed into a single inferior ophthalmic varix and then into the cavernous sinus. The superior ophthalmic vein was not involved. There was no evidence of intercranial venous abnormality in the cavernous sinus. Their patient required surgery because of intermittent exophthalmos and an incapacitating headache. Following surgical removal of the varix, the headaches disappeared, as did the cosmetic deformity. The diagnosis of orbital varix can be further delineated using orbital radiography, which may show orbital phleboliths and an enlarged orbit. Ultrasonography and CT scan show a soft tissue mass, and ultrasonography will show the mass to enlarge during

the Valsalva maneuver. Glaucoma is uncommon in this condition because of the transient nature of the malformation, and generally the glaucoma, when present, does not respond to medical therapy.[4]

Is Glaucoma Apparent in Sturge-Weber Syndrome?

Sturge-Weber syndrome, also known as encephalofacial angiomatosis or encephalotrigeminal angiomatosis, is seen with a flat facial hemangioma that follows the distribution of the fifth cranial nerve. A meningohemangioma, which may produce a seizure disorder in the child, may also be present. The meningohemangioma may be associated with calcification easily revealed by skull x-rays occurring as early as age 1 year. The association of facial hemangiomatous nevi with neurologic impairment was first clinically delineated by Sturge in 1879 in a young girl, as cited in Bodensteiner and Roach.[29] In 1922, Weber wrote the first report of the radiologic features of the syndrome. In this condition, the classic manifestations include the facial port-wine stain, a contralateral hemiparesis, hemiatrophy of the brain, and mental retardation with a homonymous hemianopsia. Other features include glaucoma, dental abnormalities, and skeletal lesions. There is no clear genetic pattern, and two affected individuals almost never arise in the same family. The syndrome presents in all races and with equal frequency in both sexes. A variant of the condition is called Klippel-Trenaunay-Weber syndrome, which is seen in children who have extensive involvement of the limbs and trunk. The glaucoma seen in Sturge-Weber syndrome occurs in anywhere from 30 to 70% of patients. It may be associated with outflow obstruction by congenital malformation of the anterior chamber angle. It may be related to hypersecretion from an associated angioma of the choroid and most probably is related to the EVP of the episcleral hemangioma. The prominent neurologic features include seizures, focal neurologic defects, and mental retardation. Port-wine stains are progressive lesions, and the location of the port-wine stain predicts its response to pulse dye laser treatment. Concerning the ocular manifestations, the glaucoma is usually unilateral when the cutaneous lesion affects one side, but bilateral cases do occur. The management of the glaucoma is difficult and typically requires surgery.[7]

The visual field defects may occur as a manifestation of involvement of the cerebral cortex. A choroidal hemangioma is present in about 40% of the cases and is sometimes very subtle and difficult to identify. It typically is described as the "tomato catsup fundus." Glaucoma is especially common if there is involvement of the upper eyelids, and presents in early infancy 60% of the time. Some researchers advocate goniotomy as the best surgical option in younger patients because of its low complication rate and its reasonable success.[30] Because of the multiple etiology, other authors believe a combined trabeculotomy/trabeculectomy is best for early onset glaucoma.[31] When either of these procedures fail, the Ahmed glaucoma valve implant has been studied in a fairly large group of Sturge-Weber patients and has an acceptable success rate.[32] No matter what surgery is done, approximately 25% will experience intraoperative or early postoperative choroidal detachment resulting from a rapid expansion of the choroidal hemangioma with effusion of fluid into the suprachoroidal and subretinal spaces. Maintaining a normal to high IOP throughout the surgery through the injection of a viscoelastic material into the anterior chamber may

help prevent some of these intraoperative complications. Posterior sclerostomy, followed by anterior chamber reformation, should be performed in the event that an expulsive suprachoroidal hemorrhage occurs. Extreme caution is advised to prevent penetration of the choroid, because penetration would lead to a disastrous hemorrhage.

Is Glaucoma Caused by Orbital-Meningeal Shunts—the Dural Shunt Syndrome (DSS)?

Dural fistulas are communications between the cavernous sinus and an extradural branch of the external or interior carotid artery. The fistulas generally have lower blood flow and lower mean pressure. The clinical appearance in these patients is far less dramatic than the appearance of those with CCSF. These patients lack bruits, and have a variable exophthalmos and variable limitations of motility. However, the conjunctival episcleral vessels have the same corkscrew, arterialized appearance and the IOP is elevated. This condition is commonly seen in elderly women with no precedent history of trauma. Dural fistulas can close spontaneously and may not require treatment. All attempts should be made to control the elevated IOP with medications until the dural shunt resolves. In most of these cases, the elevated IOP is secondary to EVP and is a well-recognized feature of DSS. However, shallowing of the anterior chamber is a rare finding, as is ocular ischemia with rubeosis. Fiori et al[33] presented three cases with elevation of IOP and angle shallowing, while one case also exhibited rubeotic glaucoma. Abnormalities of vision can also occur with vascular disorders involving the occipital lobe. Arteriole and venous disease may cause loss of visual field, distortion of vision, visual hallucinations, and palinopsia. Seven patients have been so described by Kupersmith et al,[34] although there is no mention of glaucoma in these patients. These dural shunts frequently have been misdiagnosed early in the course of the disease, and conditions to be ruled out include migraines, cluster headaches, endocrine ophthalmopathy, chronic conjunctivitis, episcleritis, iritis, and orbital tumor.[35] An unusual carotid artery fistula was reported by Nagaki et al[36] in a 77-year-old woman following routine cataract surgery. At the 1-month follow-up visit, a choroidal detachment was noted in the eye and a CT scan showed enlargement of the superior ophthalmic vein. Furthermore, cerebral angiography revealed fistulas between the meningeal branch of both the internal and external carotid arteries and the cavernous sinus. Neurosurgical treatment was performed and the symptoms disappeared.

Are Carotid-Jugular Venous Shunts Associated with Glaucoma?

Atypical causes of "red eye shunt syndrome" were reported in 1961.[4] The researchers studied 14 cases of glaucoma caused by increased EVP with an extraocular origin. They believed that the fistula was from the carotid artery directly into the jugular complex, and was a low-flow fistula. They did tonographic studies in the patients and concluded that there was a relatively normal outflow facility. As cited by others, Nordman is credited by Weinreb and Karwatowski[4] with reporting intraocular vascular shunts concerning arteriole

venous fistulas, increased EVP, and glaucoma. Further detailed analysis on this subject is unavailable at this time due to a lack of translation.

Do Intraorbital Vascular Shunts Cause Glaucoma?

Arterial venous shunts in the orbit are quite rare, and most are a part of more extensive intracranial or facial arterial venous malformations (AVMs). Of over 600 orbital tumors studied by Wright,[37] only three were AVMs. These lesions were congenital with numerous large feeding arteries, a central nidus, and numerous dilated draining veins. In contrast to the AVMs, arterial venous fistulas are characterized by a single arteriovenous connection within the vascular mass. Most of these fistulas in the orbit occur after an injury to an ethmoidal artery caused by fracture of the ethmoid bone and rupture of the artery into the ophthalmic venous system. Recently, it has been reported that a spontaneous arterial venous fistula occurred in the orbit of a 73-year-old woman with a 1-year history of mild proptosis.[38] She did in fact have a glaucoma, and the hemodynamic characteristics of this fistula were quite complicated. The conclusion was that a complete analysis of the hemodynamics by means of selective cerebral angiography was needed for differential diagnosis between these conditions.

Lacey et al[39] have undertaken a systematic review of these lesions as part of a continuum of research on the subject of vascular lesions of the orbit. They presented a large collection of patients seen over a 20-year period with orbital vascular malformations studied in a variety of ways. They were specifically interested in the distensible venous malformations. What was unique about their study was that a selected group of patients underwent intraoperative venography and embolization of their malformations. Direct intralesional venography identified the extent of the lesion and the drainage pathway. Pressure was used to achieve control of outflow, which upon angiography confirmation was followed by injection of a cyanoacrylic glue mixture into the lesion to form a cast. The vascular lesion and its cast were excised in a relatively blood-free procedure. This may represent the current state of the art for dealing with these lesions. The authors comment that it is particularly important that the hemodyamics of the venous malformation be understood before embolization is performed. Occlusion of the drainage pathway of a lesion will lead to expansion or stasis within any remaining portion if it is not completely excised. Such altered hemodyamics may favor postoperative thrombosis or hemorrhage and this may be the cause of some of the more serious complications that have been seen in the past.

Do Idiopathic or Sporadic Cases of Increased EVP Occur and Cause Glaucoma?

Patients with dilated episcleral vessels with elevated IOP frequently occur with exophthalmos. These are typically caused in the conditions of carotid cavernous fistula, dural arteriovenous shunts, orbital varices, and pulsatile exophthalmos. Dilated episcleral veins without exophthalmos have been described in patients with dural arteriovenous fistulas, in familial cases, in idiopathic cases,[40] sometimes in patients with Sturge-Weber, in patients with advanced glaucoma, and in those with extraocular venous obstruction. Talsman et al[41]

reported six unilateral cases and one bilateral case of dilated episcleral veins with elevated IOP without exophthalmos. They were careful to rule out the common causes of this syndrome. Their workup included orbital venography and carotid arteriography. Inflammatory stenosis of the jugular veins and superior vena cava obstruction were ruled out on clinical grounds. Intraocular tumors were also excluded because there were no sentinel vessels. They believe that this condition is common. Moreover, the authors stressed that mistakes often occur in working up patients who have a chronic red eye and have been erroneously described as having a chronic conjunctivitis. Absence of diffuse congestion of the conjunctival vessels with elevation of IOP and accompanying glaucomatous optic disc cupping and pallor should alert the clinician to initiate a serious workup.

Are There Familial Causes of Increased EVP and Glaucoma?

Glaucoma associated with idiopathic elevated EVP was found in two members of a family and reported by Minas and Podos[42] in 1968. Both were affected unilaterally with large episcleral veins, significantly elevated EVP, raised IOP, cupping of the disc, open angles with budding shunt vessels, and glaucomatous field loss. One of the patient's mother had a similar picture in both eyes. Neither case was found to have any of the entities known to produce elevated EVP.

Does Chronic Use of Systemic and/or Topical Medications Affect the EVP and Glaucoma?

The effects of various pharmacological agents on EVP have been evaluated in numerous studies. One report on pilocarpine demonstrates decreased EVP; however, these measurements were reported relatively high and were probably unreliable.[43] Another investigator found that pilocarpine decreased EVP,[44] and a third study found that there was no effect from pilocarpine and acetazolamide on EVP.[45] Similarly, studies evaluating epinephrine's effect had equivocal results.[46,47] Clondine seems to decrease EVP, but the changes are too small to account for any change in the IOP.[48] Also, in rabbits exposed to oxygen, there was a decrease in IOP and EVP.[49] Some experiments have shown that exposure of the eye to cold decreases EVP.[50] Recently, Netland et al[51] has used calcium channel blockers in the management of low tension and open angle glaucoma. Sawada et al[52] reported prevention of visual field defect progression with brovincamine in eyes with normal tension glaucoma. An interesting study analyzing topical verapamil and decreased EVP was reported by Abreu et al.[53] They studied 20 normal human subjects in a prospective, double-masked, randomized, crossover placebo study. The authors reported that calcium channel blockers are frequently used for the treatment of various cardiac disorders including angina pectoris, cardiac arrhythmia, systemic hypertension, and Raynaud's phenomenon. The calcium channel blockers reduce vascular resistance and help prevent vasospasm by blocking the entry of calcium into the cells. The ocular effects of calcium channel blockers were studied a few years ago with a flurry of activity, and their potential clinical role became apparent, especially in treating patients with normal tension glaucoma. There is typically an arterial vasodilation with reduction of arterial blood pressure. The reduc-

tion in IOP caused by calcium channel blockers may be due at least in part to increased outflow facility, with resultant effect on EVP.

Treatment and Management

It is apparent that the treatment and management of the 17 causes of increased EVP and glaucoma is challenging and individualized. In general, management of the glaucomas would involve medical treatment first, using combinations of drug classes, advancing to laser trabeculoplasty if the angle structures are normal and accessible. Filtration surgery, generally of the guarded variety with or without antimetabolites, would be the next choice. In advanced cases, implantation of glaucoma valves with or without antimetabolites or possibly cyclodestructive procedures should be considered. There are no large studies comparing surgical procedures because these conditions are relatively uncommon and present sporadically to a variety of practitioners. We should, however, be reminded that the red eye glaucomas may be a more common cause of glaucoma than is universally recognized. A careful and thorough evaluation and treatment of the underlying cause is required.

Future Considerations

Epstein[9] in 1997 was the first to point out that there are some basic aspects concerning increased EVP that need investigation. First, his measurements have shown that reducing the IOP by filtering operations in the syndrome of open-angle glaucoma associated with elevated EVP does not change EVP. He concluded that the pressure in these vessels must be determined by something other than the rate of outflow of aqueous humor. After successful filtration surgery, aqueous humor is no longer restricted by the regular outflow system to enter the episcleral veins against the venous back pressure but is free to bypass the system and escape into the extravascular tissue at low IOP. Second, Epstein reports that in certain cases where there is increased EVP of idiopathic origins, no blood has been seen gonioscopically in Schlemm's canal either before or after surgery. This despite the fact that filtration operations have made the IOP considerably lower than the pressure in the episcleral veins on the surface of the globe. It was suggested that obstruction may lie within or beyond Schlemm's canal. Similar phenomena may be involved in the pathogenesis of reduced aqueous humor outflow, as is commonly seen with chronic elevation of EVP.

In light of the current trends to perform nonpenetrating filtering surgery,[54,55] it would be interesting to know what the EVP changes are once this "lake of aqueous" has been created in the midscleral space. Once identified, pharmacologic modulation may enhance filtration and long-term success.

Pharmacologic manipulations of the EVP in unoperated eyes are another area of active research. Abreu et al[53] did a prospective, randomized, double-masked, crossover, placebo-controlled study testing one eye of 20 normal subjects with either the calcium channel blocker verapamil or placebo. Their results indicate that a single drop and a 2-week administration of topical verapamil decreased IOP and EVP significantly, with more pronounced reduction

at the 2-week treatment than after a single dose treatment. The mechanism of the calcium channel blockers has been discussed by Netland et al[51] and Sawada et al.[52] There may be a future in this area of investigation, especially concerning the treatment of low-tension glaucoma patients. Because the calcium flux can affect the aqueous humor dynamics, there may be a hydrostatic component caused by an efferent arterial blood pressure and ciliary body perfusion and an osmotic component caused by an effect on the active secretion of sodium, calcium, and other ions by the ciliary epithelium. The mechanism may be modulation of aqueous outflow by decreasing EVP.

The complexity of the control mechanism for vascular plexus involved in episcleral venous drainage has recently been examined by Selbach et al,[5] using scanning electron microscopy of vascular resin casts of the rat and rabbit eye. They also did fluorescein immunohistochemistry to investigate the multiple neuropeptides in these areas. They discovered that the episcleral arteriovenous anastomosis connects arterioles directly with the episcleral venous plexus, which also drains the aqueous humor. The nerve fiber layer plexus around the episcleral arteriovenous anastomosis is far more dense than around the arteriovenous connections at the limbal arcade. They concluded that there is an elaborate innervation in this area that may be involved in subtle modulations of the blood flow and possibly of the aqueous humor outflow dynamics. Basic anatomic research would be helpful in humans, as well as possible pharmacologic manipulation of these various neuropeptides.

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◆ 7 ◆

Glaucoma Associated with Primary Disorders of the Corneal Endothelium

Sylvia L. Hargrave

Two conditions with disorders of the corneal endothelium are discussed in this chapter. Both iridocorneal endothelial (ICE) syndrome and posterior polymorphous dystrophy are conditions in which there is strong clinical and histopatholigic evidence that the corneal endothelial disorder is directly associated with the changes causing the glaucoma.

Definition

The ICE syndrome includes several related disorders: essential iris atrophy or progressive iris atrophy, iris nevus (Cogan-Reese) syndrome, and Chandler's syndrome. Glaucoma is an important feature of this syndrome, and the related disorders may represent a continuum of the same process. Scheie and Yanoff[1] and Yanoff[2] proposed the term ICE to group essential iris atrophy, Chandler's syndrome, and iris nevus syndrome as varying clinical manifestations of a single disease entity.

What Is Progressive (Essential) Iris Atrophy?

A form of secondary glaucoma associated with atrophy of the iris and hole formation was described by Harms[3] in 1903. The condition was termed essential iris atrophy or progressive essential iris atrophy. Progressive iris atrophy is characterized by prominent atrophy of the iris, with iris stromal and/or full-thickness iris holes. Peripheral anterior synechiae develop early, and progress both circumferentially and onto the cornea.[4] Pupillary distortion and ectropion uveae occur typically toward the most prominent anterior synechiae.[4,5] More

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specifically, progressive iris atrophy leads to two types of holes: stretch holes and melting holes. Stretch holes are formed in the iris from tractional forces between peripheral anterior synechiae on opposite sides of the anterior chamber. Melting holes may also develop in the vicinity of peripheral anterior synechiae (Fig. 7–1).

What Is the Iris Nevus (Cogan-Reese) Syndrome?

In 1969, Cogan and Reese[6] described two patients with pigmented nodules of the iris, associated with some features similar to essential iris atrophy and Chandler's syndrome. In both cases, melanoma was suspected and the eyes were enucleated. However, on histopathologic examination, the nodules were composed of benign tissue resembling iris stroma. Later studies revealed that these nodules could occur on the iris surface in association with the spectrum of changes seen with essential iris atrophy and Chandler's syndrome. As such, the condition became known as Cogan-Reese syndrome. Scheie et al[7] described similar cases with diffuse iris nevi instead of nodules on the surface of the iris. They called this condition the iris nevus syndrome.

Iris pigmented lesions ranging from multiple, pedunculated, nodular lesions to diffuse, smooth, velvety changes are present. The iris surface often loses its normal architecture and appears darker than the iris of the fellow eye. Ectropion uveae, breaks in the iris stroma, and an ectopic pupil are often present. Also, peripheral anterior synechiae, corneal edema, and glaucoma are characteristic features (Fig. 7–2).

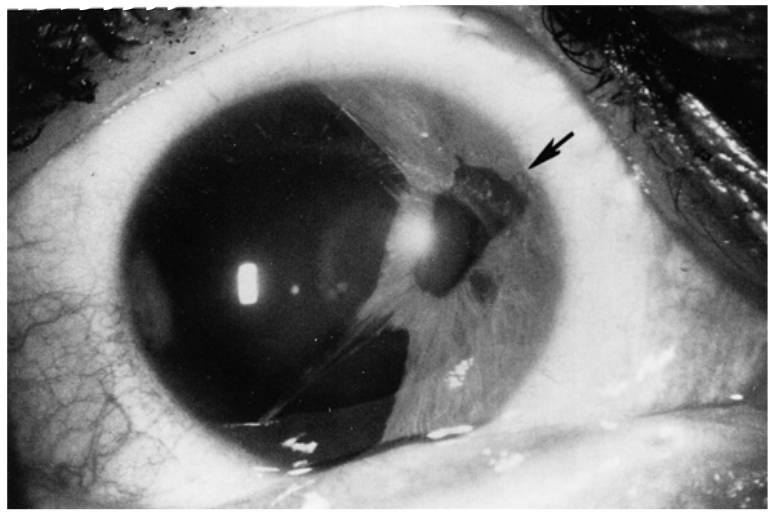


Figure 7–1. Large peripheral anterior synechiae (*arrow*) with correctopia, iris holes, and ectropion uveae in a patient with essential iris atrophy. (With permission from Miller CA, Krachmer JH: Endothelial dystrophies. In: Kaufman HE, Barron BA, McDonald MB (eds): The Cornea, 2d Ed. Newton, MA: Butterworth-Heinemann, 1997; 470.)

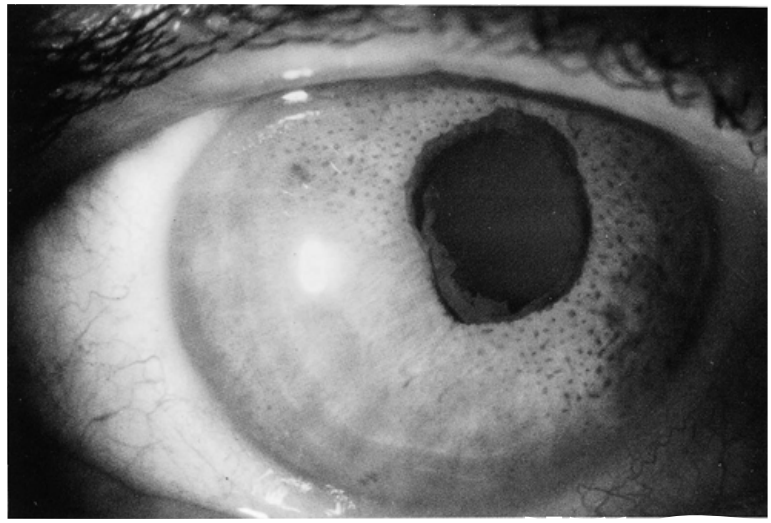


Figure 7–2. Numerous dark brown iris nodules, ectropion uveae, and correctopia in a patient with iris nevus syndrome. (With permission from Miller CA, Krachmer JH: Endothelial dystrophies. In: Kaufman HE, Barron BA, McDonald MB (eds): The Cornea, 2d Ed. Newton, MA: Butterworth-Heinemann, 1997; 471.)

What Is Chandler's Syndrome?

In 1956, Chandler[8] reported cases that were similar to essential iris atrophy but different in that changes in the iris were limited to slight correctopia and mild stromal atrophy. Here, he noticed that corneal edema appeared to be a more consistent feature and often occurred at intraocular pressures that were normal or only slightly elevated. In all cases, Chandler noted an abnormality of the corneal endothelium, which was described as having the appearance of fine, hammered silver. The condition became known as Chandler's syndrome. In both essential iris atrophy and Chandler's syndrome, glaucoma is associated with progressive closure of the anterior chamber angle. Iris atrophy is less prominent in Chandler's syndrome than in progressive iris atrophy and, when detectable, is often limited to the anterior iris stroma.[9,10] The pupil is usually round or slightly oval.

What Are the Essential Features of the ICE Syndrome?

The ICE syndrome is characterized by the proliferation and spreading of an abnormal corneal endothelial membrane across the iridocorneal angle and iris surface. This "endothelialization" often results in iridocorneal adhesions, glaucoma, pupillary distortion, iris atrophy and corneal decompensation. The primary corneal abnormality is usually unilateral, nonfamilial, and often rapidly progressive. However, cases of bilateral involvement have been described.[11] Although development of peripheral anterior synechiae is common, the accompanying secondary glaucoma is frequently more advanced than would be expected by the extent of the synechiae, presumably because of the angle endothelialization[11] (Fig. 7–3). Common manifestations of ICE syndrome also include, in addition to abnormalities of the iris, reduced visual acuity and pain.

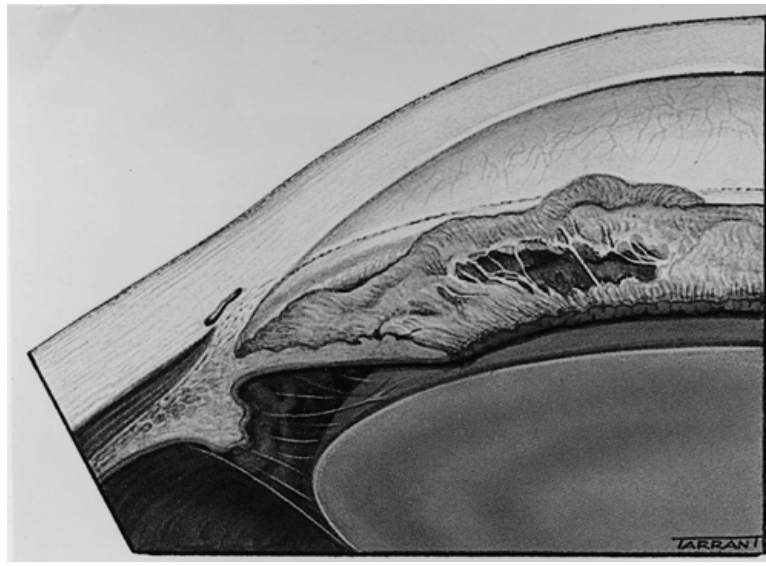


Figure 7–3. The angle in essential iris atrophy. (With permission from Kanski JJ: Clinical Ophthalmology, 2d Ed. London: Butterworth, 1989; 222.)

Epidemiology and Importance

What Is the Epidemiology of the ICE Syndrome?

Classically young to middle-aged women are affected, although men can also be affected. The male/female ratio varies from 1:2 to 1:5.[12] The typical patient is a white woman with unilateral disease and a negative family history. The onset of symptoms occurs in early to middle adulthood. Unlike posterior polymorphous dystrophy, there does not appear to be a genetic predisposition for iridocorneal endothelial syndrome. In posterior polymorphous dystrophy, a small percentage of cases have been linked to Alport's syndrome.[13] Linkage of posterior polymorphous to the long arm of chromosome 20 (20q11) was reported in a family who had 21 members with this disorder.[14]

What Were Previous Theories of Pathogenesis Regarding the ICE Syndrome?

The etiology of the ICE syndrome has been controversial since the condition was first described. Previous popular theories are enumerated in Table 7–1. It was originally thought that iridocorneal endothelial syndrome was the result of low-grade intraocular inflammation.[11] Most clinical cases reviewed did not show evidence of active inflammation, and the histologic studies have not supported a primary inflammatory cause.[2,7,15–17] Nevertheless, in true cases of essential iris atrophy, it is possible that ciliary flush may be associated with advanced bullous keratopathy. Also low-grade, chronic aqueous flare may be associated with the leaking of iris vessels; therefore, occasional evidence of intraocular inflammation does not rule out the diagnosis of the ICE syndrome.[2]

Vascular insufficiency of iris vessels has also been postulated as a mechanism of essential iris atrophy. Ischemia from sclerosis of iris vessels, congenital vascular disturbances, and vascular toxins have been proposed as theories. Anterior segment fluorescein angiography demonstrated vascular abnormalities of the iris in essential iris atrophy.[17] These abnormalities suggest the possibility of secondary alterations of the iris vasculature.

The membrane theory of Campbell[17a] was based on a clinical study of 82 patients with essential iris atrophy and a histopathologic study of 10 enucleated eyes with this condition. He postulated that essential iris atrophy begins as an abnormality of the corneal endothelium, which leads to corneal edema. The membrane sometimes extends across the angle and over the iris surface. When the membrane contracts, peripheral anterior synechiae develop and pupillary distortion occurs. The iris in the opposite quadrant undergoes thinning with variable degrees of atrophy. The aforementioned process can lead to irregular holes in the iris.

What Is the Current Theory Regarding the Etiology of the ICE Syndrome?

Leibowitz and Waring[18] have proposed that an acute pathologic insult to the corneal endothelium occurring in the second or third decade of life, for example, a viral endotheliitis, may damage the endothelium and convert it to ICE cells. These ICE cells exhibit migratory behavior and elaborate aberrant basement membrane and collagenous tissue. ICE cell alterations occur in corneas with antecedent herpes simplex keratouveitis and glaucoma.[19] Using the polymerase chain reaction to identify viral DNA in corneal specimens from patients with the iridocorneal endothelial syndrome, 16 of 25 iridocorneal endothelial syndrome patients and four of six patients with herpetic keratitis specimens were positive for herpes simplex virus.[19] When the endothelium was removed, the positive specimens became negative, thus localizing herpes simplex DNA to the endothelium. These data, although extremely compelling, do not provide definitive evidence that herpes simplex causes iridocorneal endothelial syndrome. Instead there are three possible interpretations of the findings[19] (Table 7–2).

The hypothesis that herpes simplex virus may cause the iridocorneal endothelial syndrome is consistent with the acute onset, mild inflammation, and unilaterality of this disorder. Epstein-Barr virus has also been implicated in possibly causing iridocorneal endothelial syndrome.[20] Once the endothelial cells are damaged, they exhibit migratory and secretory behavior and produce

Table 7–1. Theories of Pathogenesis of the ICE Syndrome

Inflammatory theory
Vascular theory
Primary iris defect theory
Membrane theory of Campbell

Table 7–2. Herpes Simplex Virus and the ICE Syndrome

Herpes simplex is one of the initiators of the ICE syndrome
The process producing the ICE syndrome activates latent herpes simplex virus and contributes to its pathogenesis
The processes producing the ICE syndrome activate latent herpes, but the virus is not involved in the pathogenesis of the ICE syndrome

clinical iridocorneal endothelial syndrome. The ICE cells are of variable shapes, sizes, and density. There is disagreement about whether the cells are actually epithelial-like; however, there appears to be little evidence that these cells are of direct epithelial origin.

What Is the Value of Specular Microscopy in the ICE Syndrome?

Specular microscopy contributed greatly to understanding and diagnosing the ICE syndrome.[21] As a noninvasive, painless, outpatient technique, it is used to obtain high-resolution microscopic images of the corneal endothelium. Specular microscopy performed on patients with ICE syndrome demonstrates a population of abnormal cells called ICE cells.[22] ICE cells, which are pathognomonic of ICE syndrome, are larger and more pleomorphic than normal corneal endothelial cells. These cells are observed in most cases, although they are not readily discernible in patients with severe corneal edema. In some patients, the normal endothelial architecture is replaced completely by ICE cells (total ICE), whereas in others, normal endothelial cells are only partially replaced (subtotal ICE)[22,23] (Fig. 7-4).

What Is Posterior Polymorphous Dystrophy?

Deep corneal lesions of various shapes characterize posterior polymorphous dystrophy (PPD). Nodular, grouped vesicular and blister-like lesions commonly occur.[24] Gray-white halos often surround the vesicular lesions. Flat gray-white opacities, gray thickenings of Descemet's membrane, sinuous broad bands, or clear bands with white scalloped margins also can be present.[25] These bands can be oriented vertically or horizontally and often are confused with Descemet's tears.[26] The lesions are easily seen on retroillumination. On specular microscopic evaluation, the lesions contain abnormal, pleomorphic cells, with indistinct borders and increased reflective highlights.

This dystrophy is usually transmitted as a dominant trait, but recessive patterns of inheritance have been reported.[26] It is usually bilateral, but can be asymmetric and, rarely, unilateral.[23] Congenital cases do exist and present with cloudy corneas at birth. Most patients with PPD have normal vision and are asymptomatic, making the age of onset difficult to determine. Most cases are nonprogressive, but in some cases endothelial decompensation can develop.[25]

PPD can be associated with anterior segment dysgenesis, with prominent Schwalbe's ring, iridocorneal adhesions, abnormal iris processes, iris atrophy, correctopia, and ectropion uveae.[25] Intraocular pressure (IOP) elevation occurs

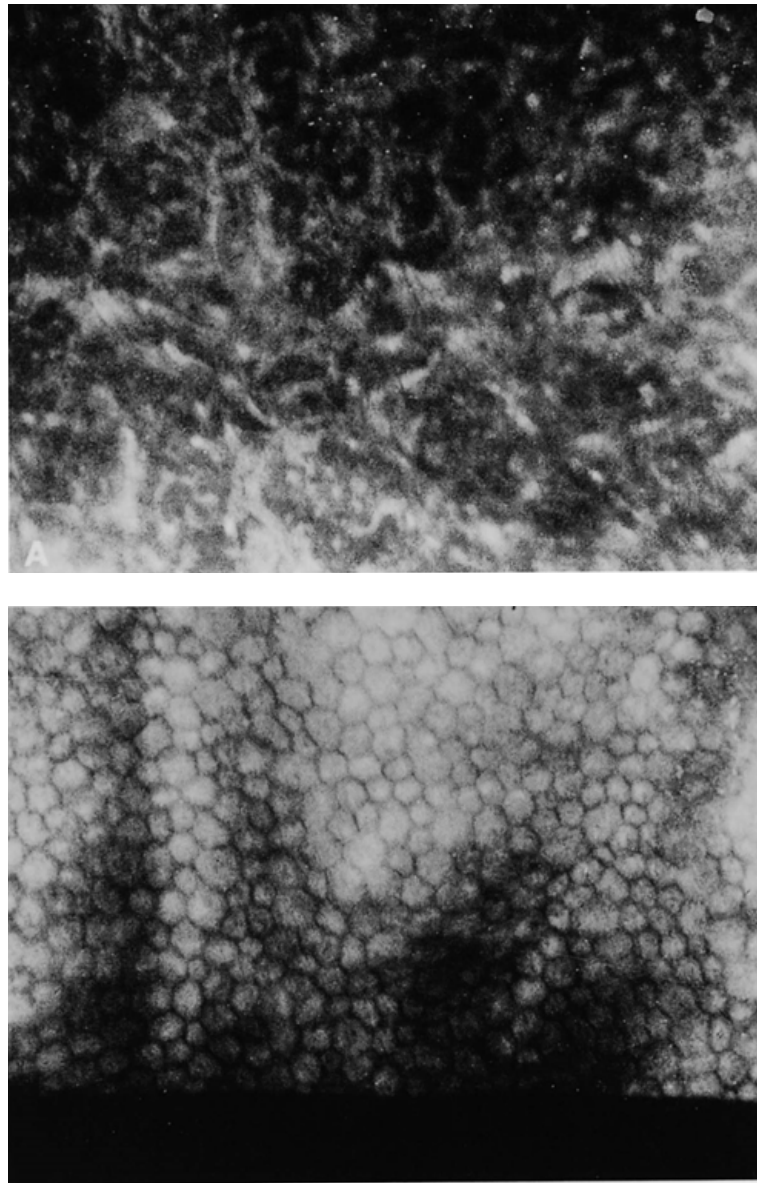


Figure 7–4. (A) Specular microscopy of the corneal endothelium in the ICE syndrome. Cell borders are obscured, resulting in loss of the normal endothelial mosaic. Note dark areas within endothelial cells. Brighter reflections are believed to be from cell borders. (B) Specular microscopy of fellow eye showing normal endothelial mosaic. (With permission from Mandelbaum S: Glaucoma associated with corneal disorders. In: Duane's Clinical Ophthalmology, Vol. 3. Philadelphia: JB Lippincott, 1993; Ch. 54F:3.)

in approximately 15% of cases.[25] The pathogenesis of PPD is unknown, but may involve endothelial cells undergoing transformation into epithelial-like cells. The angle and iris abnormalities may represent spread of these abnormal cells from the cornea.

Diagnosis and Differential Diagnosis

How Do the ICE Syndrome and PPD Differ?

The majority of ICE and PPD cases can be distinguished clinically on slit-lamp examination. PPD is a bilateral familial disorder (Table 7–3). It has been diagnosed in all age groups, usually as an incidental finding, because it is typically asymptomatic. Commonly nonprogressive, only occasionally is it associated with corneal decompensation or glaucoma. The posterior corneal abnormality shows clusters of vesicles and occasional excresences of Descemet's membrane.[8]

The universal clinical sign of the iridocorneal endothelial syndrome is a finely hammered silver appearance of all or part of the posterior corneal surface when viewed in specularly reflected light with the slit lamp.[27,28] ICE cells give rise to a hammered silver appearance on slit-lamp exam. They appear as a negative of normal endothelial cells on specular microscopy and are pathognomonic of the ICE syndrome. Classically, the diagnosis of PPD requires the presence of small, round, discrete, transparent vesicular lesions, surrounded by a ring of opacity at the level of Descemet's membrane. In some cases, however, confusion and misdiagnosis occur. Corneal edema may obscure posterior corneal details. Peripheral anterior synechiae, ectropion uveae, and secondary glaucoma may be present creating a clinical picture similar to that of iridocorneal endothelial syndrome (Table 7–4).

What Are the Associations Between Glaucoma and the Iridocorneal Endothelial Syndrome?

Few previous studies have focused on the issue of glaucoma secondary to the ICE syndrome from a clinical standpoint. Case reports indicate that glaucoma associated with the ICE syndrome is difficult to control and can result in marked visual impairment.[29–31] Therefore, it is of paramount importance to identify those patients who are most likely to develop glaucoma and devise treatment plans accordingly. The reported prevalence of glaucoma associated with the ICE syndrome is 37 to 82%.[31]

Table 7–3. Epidemiologic Features of ICE Syndrome Versus Posterior PPD Epidemiology

Feature	ICE	PPD
Laterality	Unilateral	Bilateral
Symptom onset	2d to 3d decade	Any age
Heredity	None	Autosomal dominant
Sex	Females > males	Female = male

Table 7–4. Clinical Manifestations of ICE versus PPD

Manifestation	ICE	PPD
Corneal edema	Common	Occasional
Endothelium	Guttate-like changes	Ridges, vesicles, plaques
Iridocorneal adhesions	Common	Occasional
Iris stromal atrophy	Mild to marked	Minimal or absent
Ectropion uveae	Common	Rare
Glaucoma	Very common	Rare

The diagnosis of iridocorneal endothelial syndrome should be considered in younger patients with unilateral glaucoma and confirmed by specular microscopy (Table 7–5). Glaucoma results from obstruction of the anterior chamber angle by an abnormal membrane and often closure of the angle by peripheral anterior synechiae.

One must consider posterior corneal abnormalities in the differential diagnosis of ICE. These include Fuchs' corneal endothelial dystrophy, PPD, congenital glaucoma, congenital hereditary endothelial dystrophy, trauma, and postsurgical abnormalities. Fuchs' dystrophy is a bilateral, often asymmetric condition. It can be associated with hypermetropia, short axial length, and shallow anterior chamber.[32] Women are affected more severely and 2½ times more frequently than men.[33] The earliest finding of corneal guttae is not specific for this disease.

Table 7–5. Differential Diagnosis of ICE

- Posterior corneal abnormalities
  - Fuchs' endothelial dystrophy
  - Posterior polymorphous dystrophy
  - Congenital (CHED, congenital glaucoma)
  - Traumatic (blunt, chemical, radiation)
  - Postsurgical
  - Iris atrophy
- Rieger's syndrome
  - Aniridia
  - Herpetic ocular infections
  - Iridocyclitis
  - Xeroderma pigmentosa
  - Iridoschisis
  - Congenital hypoplasia of the iris stroma
  - Iris nodules
- Melanomas
  - Iris nevi
  - Neurofibromatosis
  - Inflammatory nodules (Lisch)
  - Flocculus of the iris
  - Juvenile xanthogranuloma

CHED, congenital hereditary endothelial dystrophy.

Most patients with guttae never develop the classic signs of Fuchs' dystrophy. In some patients, the guttae lead to corneal endothelial cell loss and an inability to maintain corneal clarity. When this happens, stromal and epithelial edema usually result and can often accompany corneal scarring.

PPD is a bilateral, dominantly inherited disorder of the corneal endothelium, characterized by a spectrum of changes on the posterior corneal surface, and less commonly in the iris and anterior chamber angle.[24] Sometimes changes in the fellow eye are so minimal that it can be diagnosed as unilateral. PPD usually does not progress to corneal edema and most cases are asymptomatic. Congenital hereditary endothelial dystrophy is the most commonly encountered congenital dystrophy. It occurs in both dominant and recessive forms. The dominant form is more severe and usually present at birth.[34] The entire corneal stroma is markedly edematous and the cornea takes on a milky appearance. Throughout life, there is little variation in the clinical appearance. A spectrum of severity varying from minimal to severe can be observed in families with the dominant form of the disorder, and the parents often have PPD changes in the cornea.[35] Any form of trauma can damage the endothelium. Blunt trauma can cause ruptures of Descemet's membrane with the subsequent formation of corneal edema. During surgery, Descemet's membrane can become disinserted from the overlying stroma which can lead to corneal edema.

Iris atrophy is also included in the differential diagnosis of ICE. Essential or progressive iris atrophy is often seen with the ICE syndrome; however, it can also been seen in other forms of ocular pathology. Rieger's syndrome, aniridia, herpes, iridocyclitis, xeroderma pigmentosa, iridoschisis, and congenital hypoplasia of the iris stroma must all be considered in the differential diagnosis of essential or progressive iris atrophy. The three cardinal features of Rieger's anomaly are posterior embryotoxon with iris adhesions, hypoplasia of the iris stroma, and bilateral involvement. Ocular-associated findings include dyscoria, glaucoma, and congenital anterior synechiae. Systemic associations include Marfan syndrome, Ehlers-Danlos syndrome, Down syndrome, and oculodentodigital dysplasia.[36] Less frequently associated ocular findings include megalocornea, microcornea, aniridia, and Peters' anomaly. Herpetic keratouveitis/iridocyclitis can cause iris atrophy. Herpes simplex virus can produce uveitis, although severe herpetic uveitis is rare. In some patients, the iris may develop segmental necrosis, whereas in others, the entire iris may develop intravascular thromboses and become ischemic and necrotic.

Xeroderma pigmentosa is an autosomal recessive disorder caused by a defect in the ability to repair DNA damaged by ultraviolet light. Ocular findings include eyelid tumors, especially basal and squamous cell carcinomas. Anterior segment involvement includes conjunctival inflammation and membrane development, corneal scarring and vascularization, and anterior segment inflammation, which can subsequently lead to iris atrophy. Treatment includes prevention of tumors by the use of sunscreening agents and avoiding exposure to sunlight. Penetrating keratoplasty for corneal scarring has a poor prognosis.[37] Iridoschisis and congenital hypoplasia of the iris stroma must also be considered in the differential of iris atrophy.

Iris lesions that vary in number, size, shape, location, and texture typify the iris nevus syndrome of Cogan-Reese. Included in the differential dianosis of iris nodules are the following: iris nevi, melanomas, neurofibromatosis,

inflammatory nodules (Lisch), and juvenile xanthogranuloma. Small malignant melanomas of the iris may be impossible to differentiate clinically from benign iris nevi and other simulating lesions. Signs suggestive of malignancy include extensive ectropion iridis, prominent vascularity, sector cataract, secondary glaucoma, documented progressive growth, and lesion size. Iris melanomas range in appearance from amelanotic to dark-brown lesions. In rare instances, they assume a diffuse growth pattern, producing a syndrome of unilateral acquired hyperchromic heterochromia and secondary glaucoma. An iridectomy needs to be performed for any lesion in which there is suspected growth. If the tumor extends into the anterior chamber angle, an iridotrabeculectomy or iridocyclectomy can be performed. Enucleation appears to be indicated for eyes containing a diffuse iris melanoma, especially in glaucomatous eyes. The prognosis for most patients with iris melanomas is excellent because the biologic behavior of most of these iris tumors is usually benign. Iris nevi are discrete masses or nodules on the anterior surface of the iris. These lesions tend to be variably pigmented and composed of benign nevus cells. There is an increased incidence of iris nevi in patients with neurofibromatosis. In neurofibromatosis, one can see multiple lesions varying from tan to dark brown and about the size of the head of a pin. These lesions may be flat or elevated and are referred to as Lisch nodules.

Juvenile xanthogranuloma typically affects the uveal tract, but may also affect the conjunctiva and the corneal stroma. Yellowish-to-gray, poorly demarcated iris lesions associated with raised organ skin lesions appear within the first year of life. The lesions may be associated with spontaneous hyphema and secondary glaucoma. Histopathologically, there is a diffuse granulomatous infiltrate with lipid containing histiocytes and Touton giant cells. These lesions regress spontaneously and may also be found in the ciliary body, anterior choroid, episclera, cornea, lids, and orbit.

Treatment and Management

How Is Glaucoma Associated with the ICE Syndrome Treated?

Glaucoma in the ICE syndrome results from progressive loss of the anterior chamber angle. Formation of peripheral anterior synechiae increases with time. IOP may be higher than expected based on the area affected by the synechiae. Histologic study has confirmed that the abnormal endothelium and basement membrane often overlie the trabecular meshwork even when the angle appears open on gonioscopy.[28,31] It is postulated that this membrane consisting of ICE cells interferes with aqueous outflow even prior to the development of synechiae and contributes to elevated IOP (Fig. 7–5).

In the early stages, glaucoma may be controlled medically. Drugs decreasing aqueous production are more useful than miotics because the angle is often closed by synechiae or covered by an abnormal membrane. However, medical management has been found generally ineffective over the long term.[30,31] Argon laser trabeculoplasty is generally not effective and should be avoided. Therefore, if the IOP cannot be controlled medically, filtering surgery is indicated. Controversy exists in the reports of success rates in the ICE syndrome.

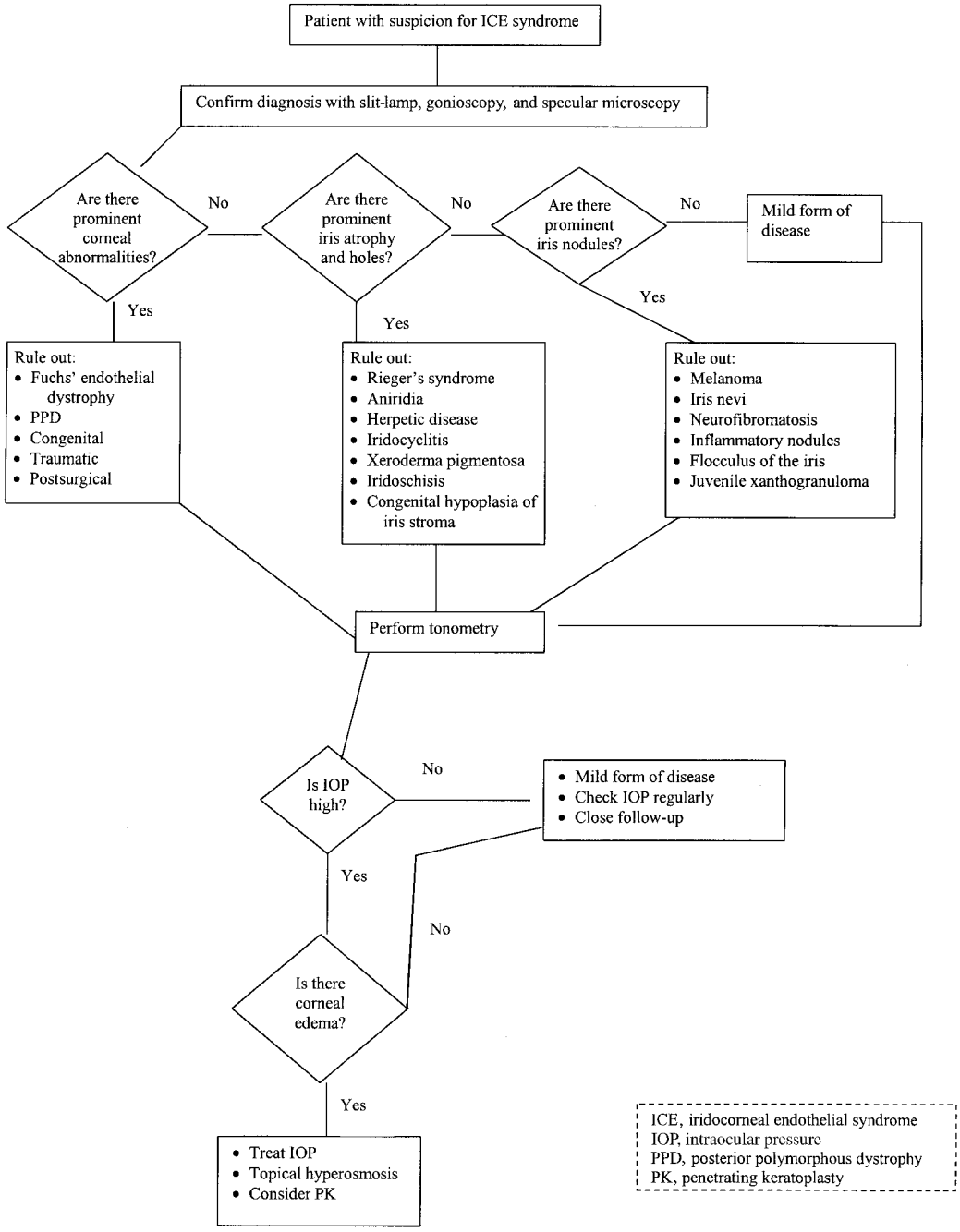


Figure 7–5. Management of a patient with the ICE syndrome.

One study reports initial success rates for trabeculectomy in the ICE syndrome as comparable to that for primary open-angle glaucoma.[38] However, others contend success rates are very poor for trabeculectomy in the ICE syndrome.[38] Late failures are usually attributed to proliferation of abnormal endothelium into the filtering bleb.[31] Progressive endothelialization of the blebs and the young age of the patients with the ICE syndrome are also common explanations for bleb failure. In these cases, another filtering procedure performed in a different location is appropriate. The success rates for repeated trabeculectomies are comparable to those of the initial procedure.[38] The use of antimetabolites and setons may improve the results of secondary filtering procedures in recalcitrant cases.[39] Vigorous control of inflammation following filtering procedures is necessary to help avoid bleb failure. Because the viral etiology of this syndrome has yet to be definitively confirmed, topical and systemic antiviral treatment may be therapeutic.[40,41]

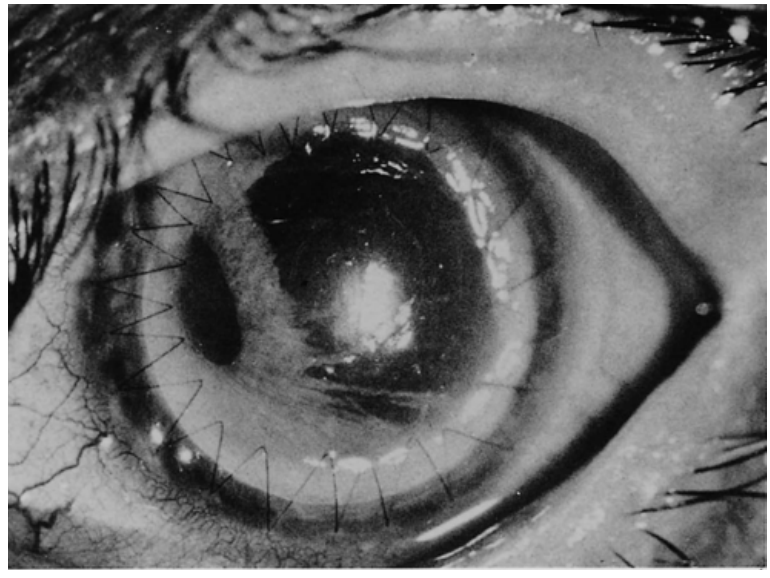
Patients with corneal edema may benefit from lowering of the IOP. However, filtering surgery cannot be recommended solely in an attempt to resolve the corneal edema.[42] The cornea can remain edematous even at the lowest achievable levels of IOP. Hypertonic saline drops are often helpful for mild corneal edema. If visually significant corneal edema is present after IOP has been lowered medically, then penetrating keratoplasty is usually required (Fig. 7–6). If the IOP remains controlled, the prognosis for the corneal graft is good.[43] Recurrences of the endothelial abnormalities that characterize the ICE syndrome have not been noted to develop on the donor cornea.[27,43]

What Is the Role of Penetrating Keratoplasty in the Management of the ICE Syndrome?

Corneal edema, even at normal intraocular pressures, predominates in Chandler's syndrome. Early corneal edema may respond to topical hyperosmotic solutions or ointment. Lowering the IOP improves corneal clarity and visual acuity in some patients. Penetrating keratoplasty is indicated in cases in which corneal edema significantly reduces vision, precludes visualization of the optic nerve, or causes pain from bullous keratopathy, recurrent corneal erosions, or secondary infectious keratitis.[43–45] The success rate for penetrating keratoplasty in the ICE syndrome has generally been favorable despite poor overall clinical prognosis for the disorder.[43–45] The role of surgical pupilloplasty and lysis of peripheral anterior synechiae at the time of penetrating keratoplasty remains unclear.

What Is the Summary of Treatment of the ICE Syndrome?

The most important problem to treat in the ICE syndrome is elevated IOP. Treatment is more difficult than that of chronic open-angle glaucoma because an abnormal membrane and peripheral anterior synechiae cover the trabecular meshwork. If the IOP is controlled, corneal edema is often less severe. However, corneal edema can be visually significant and warrant penetrating keratoplasty in a small percentage of cases. Penetrating keratoplasty is usually successful in the variants with predominantly corneal disease; however, it may be less successful in those cases with extensive iris disease and glaucoma.



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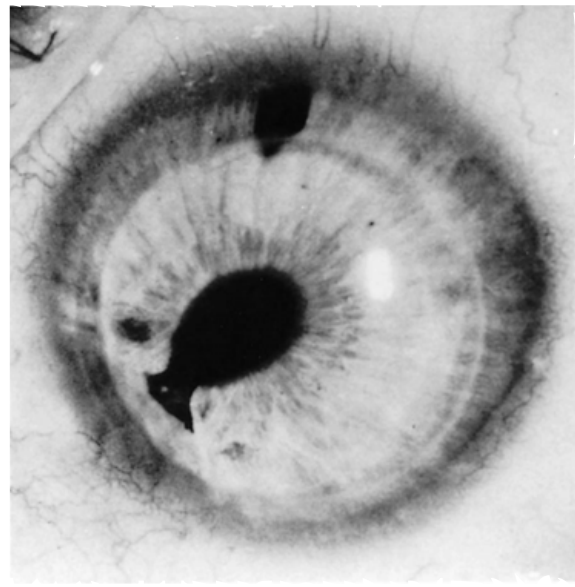

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Figure 7–6. (A) Clear right corneal graft 1 month after penetrating keratoplasty for decompensated cornea due to iridocorneal endothelial syndrome. Marked iris dissolution and hole formation is apparent. (B) Left corneal graft for iridocorneal endothelial syndrome remains clear for 9 years after penetrating keratoplasty. (With permission from Crawford GJ, Stulting RD, Cavanagh HD, et al: Penetrating keratoplasty in the management of iridocorneal endothelial syndrome. Cornea 1989;8:34–38.)

Table 7–6. Glaucoma Associations with Corneal Disease

1. Primary corneal endothelial disorders
   - Iridocorneal endothelial syndrome
2. Anterior segment developmental abnormalities
   - Peter's anomaly
   - Rieger's syndrome
   - Anterior chamber cleavage syndromes
3. Congenital
   - Congenital hereditary endothelial dystrophy
   - Congenital hereditary stromal dystrophy
   - Posterior polymorphous dystrophy
4. Corneal and/or intraocular infectious/inflammatory processes
   - Herpes simplex/herpes zoster keratitis/keratouveitis
   - Any severe iritis
   - Chandler's syndrome
5. Penetrating keratoplasty performed on eyes developing glaucoma

Generally, we do not treat iris atrophy or ectopic pupils unless the pupil is significantly eccentric to interfere with visual acuity. In these cases, surgical or yttrium-aluminum-garnet (YAG) laser iridoplasty may be of value.

Future Considerations

Future considerations include morphometric characteristics of the contralateral corneal endothelium in the ICE syndrome. Luca-Glass et al[37] have tried to determine whether subclinical morphologic abnormalities exist in the contralateral, clinically uninvolved eye of patients with the ICE syndrome. Their data suggest the corneal endothelium of the clinically uninvolved, contralateral eye may have increase pleomorphism, expressed as a relatively low percentage of hexagonal cells. They found that this issue is important when considering the various hypotheses proposed to explain the pathogenesis of the disease. More studies are needed to further unravel this mystery.

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◆ 8 ◆

Glaucoma Associated with Inflammation

George Shafranov and Joern B. Soltau

Definition

How Is Glaucoma Associated with Inflammation Defined?

Inflammatory ocular conditions like keratitis, episcleritis, scleritis, and uveitis may cause elevated intraocular pressure (IOP) by compromising the outflow of aqueous humor. Whether or not increased secretion of aqueous plays any role is still controversial.[1,2] The anterior chamber angle may be open or occluded. The IOP may be elevated acutely and/or chronically. This chapter discusses each inflammatory condition separately.

GLAUCOMA ASSOCIATED WITH KERATITIS

Definition

How Is Glaucoma Associated with Keratitis Defined?

IOP elevation may be encountered in any active corneal inflammatory condition.[3] If the elevated IOP is causing optic nerve damage and visual field loss, then the diagnosis of glaucoma secondary to corneal inflammation can be made. This implies that the elevated IOP does not necessarily lead to optic nerve damage, that is, glaucoma. This further implies that elevated IOP associated with corneal inflammation does not always need to be lowered with antiglaucoma agents. After treatment and resolution of the underlying inflammatory condition, the IOP may return to the normal level without having caused any damage to the optic nerve.

Clinical Pathways in Glaucoma. Edited by Zimmerman and Kooner.
Thieme Medical Publishers, Inc., New York © 2001.

What Is the Cause of the Elevated IOP in Keratitis?

Anterior uveitis often accompanies keratitis. Inflammatory cells may occlude the trabecular meshwork and thus decrease aqueous outflow. Posterior synechiae may develop as a result of inflammation and cause pupillary block. Peripheral anterior synechiae may cause IOP elevation, not only acutely but also chronically, even after the inflammation subsides.[3]

After chemical burns, the IOP may rise rapidly initially secondary to shrinkage of the outer coats of the eye, followed by a second slow phase of IOP elevation probably mediated by an intraocular release of prostaglandins.[4,5] IOP elevation usually occurs if the keratitis involves the corneal stroma, such as infectious keratitis secondary to herpes simplex,[6] bacterial and fungal keratitis, and an immune response to *Treponema pallidum*.[6–10] A shallow anterior chamber may develop in keratomycotic malignant glaucoma.[11] Fungi can also penetrate the cornea and directly invade the trabecular meshwork.[12]

Direct involvement of the trabecular meshwork by the underlying inflammatory disease process is the main cause of elevation of the IOP.[8,13] Increased corneal thickness secondary to corneal edema may lead to closure of the anterior chamber angle. Formation of anterior synechiae with secondary angle closure may also be encountered. Mechanisms of IOP elevation can also include secondary iridoschisis,[14] keratouveitis,[6] and open-angle glaucoma superimposed on old inflammatory changes, involving endothelialization and glassy membrane in the angle, which are refractory to medical treatment. This condition usually requires filtering surgery.[8] Reversible angle-closure glaucoma associated with anatomically small anterior segments responds well to iridectomy.[8,10] Sundmacher and Neumann-Haefelin[15] found that secondary glaucoma was present in all herpes simplex keratitis patients with corneal endothelial disease and/or anterior uveitis who had herpes simplex virus isolated from the aqueous. Similarly, adenovirus type 10 has been associated with keratoconjunctivitis, pharyngitis, and transient increase in IOP.[16]

Epidemiology and Importance

How Often Is Keratitis Associated with Increased IOP?

Keratitis by itself is not commonly associated with elevated IOP. However, when herpes simplex keratitis was associated with uveitis, almost a third of the patients developed IOP elevation and 10% had glaucomatous damage.[6]

About 40% of patients with herpes zoster ophthalmicus can have uveitis, and more than 10% of those patients may have associated glaucoma.[17] Another study showed that every third patient (five out of 14) with herpes zoster keratouveitis had IOP elevation.[18] Combination of keratitis and IOP elevation may be seen in patients with acute primary angle-closure glaucoma. These patients may develop secondary keratouveitis and keratic precipitates.[19] Possible mechanism of the inflammation is likely profound endothelial damage from elevated IOP. Hypopyon is also likely to be present in these eyes,[19–21] secondary to ischemic iris necrosis.

Diagnosis and Differential Diagnosis

How Is Glaucoma Associated with Keratitis Diagnosed?

An accurate history is important to find the etiology and to differentiate between an acute and a chronic condition. Slit-lamp examination facilitates evaluation of possible corneal infiltration and anterior chamber reaction. Subsequent use of fluorescein helps in evaluating the corneal surface. Gonioscopy should be performed, if possible.

What Is the Differential Diagnosis of Glaucoma Associated with Keratitis?

In a patient presenting with keratitis and IOP elevation, the following conditions should be differentiated: corneal abrasion,[22] recurrent erosion syndrome,[23] herpes simplex keratitis, herpes zoster keratitis, and angle-closure glaucoma causing corneal edema. Leprosy may need to be excluded when a patient presents with glaucoma, keratitis, and bilateral uveitis.[24]

Treatment and Management

How Is Glaucoma Associated with Keratitis Managed?

Treatment of keratitis associated with increased IOP is directed against the underlying etiology and includes administration of aqueous suppressants. One of the suggested therapeutic regimens for herpes simplex keratitis associated with glaucoma consists of antivirals, steroids, cycloplegics, and aqueous suppressants.[15] The treatment can be difficult, especially if angle closure with synechiae is present. In these cases, filtering surgery[8] or implantation of a drainage device might be necessary.

Future Considerations

In stromal keratitis induced by herpes simplex virus (HSV), the immune response contributes to corneal scarring and neovascularization. To analyze the efficacy of topically applied cyclosporin A (CsA) in patients with HSV keratitis, Heiligenhaus and Steuhl[25] performed a prospective study in 18 patients with HSV stromal keratitis. The authors treated eyes with CsA eyedrops and acyclovir ointment. Keratitis resolved with CsA treatment in 10 of 14 patients with nonnecrotizing keratitis and in two of four with necrotizing keratitis. One-third of the patients treated with CsA developed persistent or progressive inflammation and required combined CsA and corticosteroids. The only complication from the use of CsA was toxic epitheliopathy. HSV stromal keratitis can be treated successfully with CsA eyedrops, especially in nonnecrotizing keratitis. In patients with steroid-induced glaucoma, herpetic corneal ulcers may be

primary candidates for use of the CsA.[25] Further studies will evaluate the use of topical CsA in the treatment of herpetic keratitis associated with glaucoma.

GLAUCOMA ASSOCIATED WITH EPISCLERITIS

Definition

How Is Glaucoma Associated with Episcleritis Defined?

Intraocular pressure elevation is not seen frequently with episcleritis. Similar to all inflammatory conditions, elevated IOP does not always cause optic nerve damage and visual field loss, and does not always need to be lowered with IOP-lowering agents. After observation and/or treatment, the underlying inflammatory condition usually resolves, and the IOP typically returns to normal level without damaging the optic nerve.

Epidemiology and Importance

How Often Does Episcleritis Present with Elevated IOP?

Episcleritis is rarely associated with elevated IOP.[26,27] Few cases have been reported in the literature.[28,29] Glaucoma was found in 9% (9 out of 100) of the eyes with episcleritis in a recent retrospective study of patients with episcleritis, and none of the patients had a history of glaucoma.[30] Four of those nine patients were using topical steroids for recurrent episcleritis of the initial exam. Glaucoma was more common in patients with recurrent episcleritis but was infrequent with bilateral involvement.[30] Possible elevation of the episcleral venous pressure does not seem to influence the IOP, but this is still controversial.[26,28,31]

Diagnosis and Differential Diagnosis

How Does Episcleritis Present?

Episcleritis is a benign condition that presents with acute onset of redness, mild discomfort, and infrequently mild pain. It is often recurrent and is bilateral in every third patient with episcleritis. It occurs in young adults[32] and appears to be twice as common in females.[30] Visual acuity is usually not affected; the redness is commonly limited to a scleral sector, but occasionally can be diffuse. Conjunctival and episcleral vessels are engorged and can be moved over the sclera. The cornea is usually clear, and the anterior chamber is quiet.[32,33] Episcleritis is mostly idiopathic; however, an associated systemic disease is found in a third of the cases,[26,30,32] the most common being atopy.[30] Rosacea can also cause episcleritis.

What Is the Differential Diagnosis of Glaucoma Associated with Episcleritis?

Inflammation of the sclera and episclera may be associated with systemic diseases. Sainz et al[29] evaluated ocular complications and specific systemic disease association in 266 patients (358 eyes) with different types of scleritis and episcleritis; 37% of patients with scleritis developed decrease in vision, 42% had an associated anterior uveitis, 14% developed peripheral ulcerative keratitis, 13% developed glaucoma, 17% formed cataracts, and 6% had fundus abnormalities. More than half of the patients (57%) had an associated disease. These findings were more typical for necrotizing scleritis. In contrast, only 2% of patients with simple and nodular episcleritis developed some degree of visual loss, 11% had an associated anterior uveitis, 4% developed glaucoma, and 2% formed cataracts. Every third patient had a specific disease association.[29]

Treatment and Management

How Is Episcleritis Treated?

Treatment of episcleritis is directed at the underlying cause if one is identified (i.e., elimination of irritants and application of mast cell stabilizers for atopy, doxycycline for rosacea).[30] Because episcleritis is a self-limited condition, nonspecific treatment is not necessary if the patient is asymptomatic. Idiopathic symptomatic episcleritis can be treated with cold compresses, iced artificial tears,[30] and topical vasoconstrictors. Treatment of episcleritis with topical flurbiprofen has not been shown to be more effective than placebo.[34] Treatment of recurrent episcleritis with low-dose oral nonsteroidal antiinflammatory drugs (NSAIDs) is effective[30] and has not been associated with IOP elevation.

Topical treatment with the relatively new NSAID aminothiazole hydrochloride 0.1%[35,36] was effective in reducing inflammation in mild episcleritis within the first week of administration of the drug. It was not effective against severe episcleritis. There was no effect on IOP.[37]

How Is Glaucoma Associated with Episcleritis Managed?

There are different mechanisms for elevated IOP in a patient with episcleritis. Each condition is managed accordingly.

How Is Steroid-Induced Elevation of IOP Managed?

Corticosteroids are always effective in reducing the symptoms of episcleritis,[34,38,39] but IOP should be monitored weekly and therapy with steroids should not be continued longer than a few weeks[30,32] (see also Chapter 15).

How Is Elevated IOP with Open Anterior Chamber Angle Managed?

There are almost no reported causes in the literature of an association of episcleritis with IOP elevation. Watson[40] did not find any evidence of glaucoma in 192 eyes of 117 patients with episcleritis. Harbin and Pollack[28] described two patients with episcleritis and IOP elevation. One of the four eyes had anterior uveitis. The authors assume that in the other 3 eyes the inflammation was limited to the angle structures, especially the trabecular meshwork, causing impairment of the aqueous outflow without involving the iris and ciliary body vasculature. The low facility of outflow implies that the increased episcleral venous pressure was not the mechanism of IOP elevation. These patients respond to aqueous suppressants and treatment with topical steroids.[28]

How Is Elevated IOP Associated with Angle Closure Managed?

Acute angle closure is a rare complication of episcleritis. These eyes should respond to standard therapy for acute angle closure with neodymium:yttrium-aluminum-garnet (Nd:YAG) laser iridotomy or peripheral iridectomy[41] (see also Chapter 5).

How Is Preexisting Open-Angle Glaucoma Associated with Episcleritis Managed?

Patients with preexisting open-angle glaucoma have a higher chance of being steroid responders and should therefore be monitored closely when treated with topical steroids.[42] Among comparable age groups, the steroid-induced IOP elevation was always greater in glaucomatous than in normal eyes.[43]

Future Considerations

The development of soft steroids that will treat inflammation without elevation of IOP will greatly aid in the management of episcleritis. Recent arrivals in this group are loteprednol and rimexolone.

GLAUCOMA ASSOCIATED WITH SCLERITIS

Definition

How Is Glaucoma Associated with Scleritis Defined?

As in all inflammatory conditions associated with IOP elevation, glaucoma associated with scleritis must meet the criteria of glaucomatous damage: glaucomatous optic nerve, visual field loss, and IOP elevation developing secondary to scleritis.

How Does Scleritis Present?

Scleritis is a serious and damaging ocular condition. It usually presents with severe pain, radiating to the orbit, forehead, cheekbone, and teeth. The patient complains of photophobia and insidious decrease of vision. The eye is red due to injection of scleral, episcleral, and conjunctival vessels. The sclera may be affected only in one sector or diffusely. As opposed to episcleral vessels, the affected scleral vessels cannot be moved with a cotton swab. The scleritis can be recurrent and is associated with a systemic disease in approximately 50% of cases. It can be divided into anterior and posterior scleritis.[32,44]

Epidemiology and Importance

How Often Is Scleritis Associated with Elevated IOP?

Most studies have found that 12% to 13% of patients with anterior scleritis present with glaucoma;[29,32,41] 20% of those eyes may also have associated keratitis.[26] Elevated IOP was detected in 18.7% of eyes with rheumatoid scleritis.[27] However, 50% of eyes enucleated for scleritis also had glaucomatous optic neuropathy.[41] Episcleritis normally does not progress to scleritis, except in the case of herpes zoster, which may start as an episcleritis and reappear 3 months later as a scleritis at the same site.[26]

Wilhelmus et al[45] reviewed 92 enucleated eyes with histopathologic evidence of scleral inflammation. They also examined 114 eyes from 81 patients with scleritis. Almost half of the enucleated eyes and every fifth eye in examined patients showed evidence of increased IOP, the most common causes of which were damage to the trabecular meshwork from iridocyclitis, overlying corneoscleral inflammation, or peripheral anterior synechiae. Other causes included topical corticosteroid use; angle neovascularization in enucleated, but not in clinically observed, eyes; and posterior scleritis with secondary angle closure.

Sainz and co-workers[46] found that in 42% of patients with scleritis, inflammation may extend to the anterior uveal tract and cause anterior uveitis, with consequent development of glaucoma in 19% of eyes in that group.[46] Posterior scleritis is typically not associated with glaucoma, but angle closure secondary to choroidal effusion has been reported in the literature.[45–51] In 5% of patients with scleritis, the elevated IOP can be related to the administration of corticosteroids used to treat the underlying condition.

Why Is the Intraocular Pressure Elevated in Scleritis?

There are several mechanisms for raised pressure in patients with scleritis. These patients may present with any of the following four clinical features:

Elevation of IOP with Open Anterior Chamber Angle

The IOP may be elevated in the presence of an open anterior chamber angle. This may be caused by (1) increased resistance to outflow from inflammation in

the trabecular meshwork;[45] (2) preexistent abnormalities in outflow pathways that are impaired by perilimbal inflammation and edema; (3) abnormal steroid response;[45,52] and (4) elevated episcleral venous pressure.[53]

Acute uveitis causing damage to the trabecular meshwork and occlusion of the trabecular meshwork by inflammatory cells was the main mechanism of IOP elevation in pathologic studies of the eyes with glaucoma and scleritis.[45] Discontinuation of steroids decreased IOP in the eyes with induced ocular hypertension due to abnormal steroid response.

Wilhelmus and associates[45] reported that 4 out of 92 eyes enucleated for scleritis had an open angle and did not demonstrate any trabecular meshwork abnormalities. They were thought to have primary open-angle glaucoma. All these eyes had lymphocytic cuffing around the intrascleral outflow channels with perivasculitis of the anterior uvea, which may have caused increased resistance to aqueous flow. The possible increase of the episcleral venous pressure has been argued as a cause of the elevated IOP.[45]

Elevation of IOP Associated with Angle Closure

Angle closure secondary to peripheral anterior synechiae may cause elevated IOP. However, this is unlikely to occur in scleritis without concurrent uveitis.[45] Acute angle closure may occur in eyes with posterior scleritis secondary to choroidal effusion and forward rotation of the iris-ciliary body.[47–51]

Pupillary Block Secondary to Posterior Synechiae

Concurrent uveitis may cause formation of posterior synechiae with seclusio pupillae and iris bombé.

Neovascular Glaucoma

Neovascular glaucoma can occur in eyes affected by scleritis. In a series of 92 eyes enucleated for scleritis, 14 eyes (15%) had a neovascular membrane covering the anterior chamber angle.[45]

Diagnosis and Differential Diagnosis

How Is Glaucoma Secondary to Scleritis Diagnosed?

Typically, the diagnosis is based on clinical examination.[26] In addition to routine laboratory blood tests, skin tests, radiologic tests, electrodiagnostic tests, and tissue biopsy for uveitis workup, patients should have documented damage to the optic nerve secondary to the IOP elevation from scleritis.

What Is the Differential Diagnosis of Glaucoma Associated with Scleritis?

The differential diagnosis of scleritis is crucial for early and effective treatment. The recognition of necrotizing scleritis is particularly important because it is

frequently associated with ocular complications and a bad ocular prognosis. Scleritis associated systemic vasculitis indicates its generalization with potential development of lethal systemic complications. Only the early diagnosis and an adequate aggressive therapy can preserve ocular functions and the patient's life. Conventional steroid therapy generally fails to control the inflammatory activity in necrotizing scleritis. However, application of nonsteroidal immunosuppressive drugs has been shown to control the vasculitic conditions in the majority of cases, to improve ocular prognosis, and to reduce mortality.[54] The dry eye syndrome secondary to Sjögren's syndrome or medication use must be differentiated and treated appropriately to avert sight-threatening complications and to alleviate substantial discomfort.[55]

Acute rheumatic fever in a young child with fever, sore throat, joint pains, and malaise can present together with scleritis, uveitis, and glaucoma. Patients may have an increased antistreptolysin-O antibody titer. Testing for antistreptococcal antibody is indicated in diagnosing rheumatic fever complicated with scleritis, uveitis, and glaucoma.[56]

Treatment and Management

Treatment of glaucoma secondary to scleritis is often difficult and complicated. It usually includes topical and systemic corticosteroids and NSAIDs. Aqueous suppressants are applied to lower the IOP. Discontinuation of steroids that are used to treat the underlying scleritis is not always feasible even if an abnormal steroid response is suspected. If medical therapy completely fails to control the IOP, trabeculectomy or implantation of a drainage device may be necessary.

Acute angle closure can be treated with standard therapy regimen (see also Chapter 5). Formation of posterior synechiae can be prevented with the use of mydriatics. Iris bombé is treated initially with mydriatics. If this is unsuccessful, laser pupilloplasty can be tried, or a peripheral iridotomy/iridectomy can be placed.

Future Considerations

Identification and description of inflammatory mechanisms will be necessary for the development of new medications that will control intraocular inflammation without affecting the IOP.

GLAUCOMA ASSOCIATED WITH UVEITIS

Definition

What Is Uveitic Glaucoma?

Glaucoma can be called *uveitic glaucoma* only when the glaucomatous optic nerve damage, glaucomatous visual field defects, and IOP elevation associated with uveitis have been documented. More specific terms such as *hypertensive uveitis* can be used for conditions not meeting all the aforementioned criteria.[57]

What Is the Etiology of Glaucoma Associated with Uveitis?

Elevated IOP commonly complicates any type of uveitis. The inflammatory cells and mediators, as well as the corticosteroids used in the treatment of the uveitis, all contribute to the pathogenesis of uveitic glaucoma by altering the anatomy of the anterior chamber and its angle and by influencing aqueous production and outflow. These changes disrupt the homeostasis of IOP control. Changes in the angle can be acute, such as in secondary angle closure with pupillary block glaucoma, or chronic, such as combined steroid-induced and secondary open-angle glaucoma.[57]

Uveitic glaucoma may occur by acute angle closure due to iris bombé caused by posterior synechiae, chronic angle closure due to peripheral anterior synechiae, open-angle glaucoma due to obstruction and/or inflammation of the trabecular meshwork, or any combination of the above. If secretory hypotony develops, it may mask compromised outflow. Corticosteroids for treatment of the uveitis may cause an elevation of IOP. Thorough differential diagnosis of the pathophysiologic mechanisms involved in uveitic glaucoma is absolutely essential for successful management of these conditions.[58] In uveitic glaucoma the optic neuropathy is caused by an increased IOP, which by itself is elevated due to complications caused by inflammation of the uvea. In addition, inflammatory conditions, such as sarcoidosis, can cause direct damage to the optic nerve.[59]

Does Uveitis in a Glaucomatous Eye Always Mean Uveitic Glaucoma?

No, even though the differentiation between uveitic glaucoma and glaucoma with uveitis can be difficult, it is important to consider angle closure or open-angle glaucoma and its subtypes in the differential diagnosis of uveitic glaucoma. Pseudoexfoliation, neovascularization, and laser or intraocular surgery may cause secondary inflammation due to disturbance of the blood–aqueous barrier.

Epidemiology and Importance

How Common Is Uveitic Glaucoma?

The epidemiology of uveitic glaucoma is difficult to define because different investigators define glaucoma and uveitis differently in their studies. The frequency of glaucoma in uveitis differs among the different uveitis entities. Anterior uveitis represents 27[60] to 45%[61] of all uveitis syndromes, achieving 0.2 to 0.4% lifetime cumulative incidence in the general population.[62] Human leukocyte antigen HLA-B27–positive acute anterior uveitis is associated with a more serious prognosis when compared to HLA-B27–negative acute anterior uveitis.[63]

Panek and associates[64] noted that 20 out of 76 patients with chronic uveitis developed secondary glaucoma, and among 24 patients with acute uveitis secondary glaucoma was found in three patients. The authors concluded that their results confirmed the concept that secondary glaucoma is a management problem in patients with chronic rather than acute uveitis. In another study, out of 340 children with anterior uveitis 46 (13.5%) developed secondary glaucoma.[65]

Is the Elevated IOP More Often Associated with a Closed or Open Anterior Chamber Angle?

The elevated IOP in eyes with uveitis is more often associated with open anterior chamber angles than with angle closure. Frequently the elevated IOP is caused by clogging of the trabecular meshwork with inflammatory cells without developing peripheral anterior synechiae, and rarely by precipitates on the trabecular meshwork without signs of inflammation.[66,67] IOP elevation may be caused by obstruction of aqueous outflow by serum components,[68] or swelling of the stroma,[69] or inflammation of the endothelium of the trabecular meshwork. Glaucoma commonly complicates herpetic uveitis by causing trabeculitis with obstruction of the trabecular meshwork with inflammatory cells.[6,70,71] However, closed anterior chamber angles can also be encountered. Several mechanisms of angle closure are possible:

Primary Angle Closure

Primary angle closure occurs primarily in predisposed eyes with narrow angles. It is usually difficult to establish what is the primary event.

Secondary Angle Closure

Peripheral Anterior Synechiae
Inflammatory cells accumulating in the drainage angle of the anterior chamber adhere to the trabecular meshwork and peripheral iris causing peripheral anterior synechiae (PAS). Iris neovascularization that may develop from chronic inflammation can also contribute to the formation of PAS. This leads to occlusion of the drainage angle and thus elevation of the IOP.

Forward Rotation of the Ciliary Body
Edema of the ciliary body may rotate the lens-iris diaphragm forward. The anterior chamber becomes shallow and the angle closes.[49]

Pupillary Block and Posterior Synechiae
Formation of inflammatory adhesions between the iris sphincter and the lens, or the vitreous in the aphakic patient, or the intraocular lens (IOL) in the pseudophakic patient causes the interruption of aqueous flow from the posterior to the anterior chamber.[72]

Diagnosis and Differential Diagnosis

How Is Glaucoma Associated with Uveitis Diagnosed?

The diagnosis of active inflammation is based on detection of inflammatory cells in the aqueous and/or vitreous. Flare in the anterior chamber is evidence of vascular incompetence and is usually chronic.[73] Careful gonioscopy is absolutely essential for making the correct diagnosis. The presence of precipitates on the trabecular meshwork and scattered peripheral anterior synechiae even in the absence of obvious uveitis is a sign of ocular inflammation.[66]

What Is the Differential Diagnosis of Glaucoma Associated with Uveitis?

Adenoma of nonpigmented epithelium of the ciliary body can present as anterior uveitis and glaucoma.[74] Uveitis glaucoma hyphema syndrome[75,76] together with lens-induced uveitis and phacolytic glaucoma[77] should be included in the differential diagnosis.

Severe corneal edema in aphakic eye can develop secondary to neovascular glaucoma.[78] Nonpenetrating trauma to the eye can induce nonspecific intracameral inflammation with cells, flare, fibrin, and increased IOP.[79]

Rarely, inflammatory glaucoma may present with acute onset of IOP elevation and inflammatory precipitates on the trabecular meshwork in otherwise quiet eyes. This condition is called Grant's syndrome. Ultrasound biomicroscopy can be useful for imaging inflammatory precipitates in the angle. These patients do not respond well to typical IOP lowering agents but have excellent response to topical steroids. This condition is often bilateral and tends to recur. It may have a systemic association with sarcoidosis. Grant's syndrome should be considered as a possible diagnosis of elevated IOP in clinically quiet eyes.[66,67]

Treatment and Management

Treatment is simultaneously aimed at the underlying uveitis, preventing future complications that may cause IOP elevation and/or vision loss, and at lowering the IOP if necessary to prevent glaucomatous optic neuropathy. Decreased inflammation in the trabecular meshwork can increase aqueous drainage and thus lower IOP. The reverse, however, might be true if the ciliary body recovers its secretory function with decreasing inflammation. Medical and surgical options are available (Fig. 8–1).

What Is the Medical Therapy?

There are several options for the medical therapy of this condition:

Corticosteroids

Corticosteroids are the mainstay of therapy for uveitis. Topical steroids are effective for anterior segment inflammation but not against posterior and intermediate uveitis in the phakic eye. However, they also have the potential to raise the IOP (see also Chapter 15) and cause ocular complications such as fungal keratitis.[80]

Dexamethasone and prednisolone are the most potent topical corticosteroids available, but have an increased risk of IOP elevation. Fluorometholone and medrysone are weaker steroids, but are less likely to produce IOP elevation. Newer "soft steroids" like loteprednol and rimexolone seem to have the properties to treat ocular inflammation effectively with less risk of affecting the IOP.[81,82]

Periocular injections provide effective treatment for posterior and intermediate uveitis. Hydrocortisone subconjunctival injection dosages range from 50 to 125 mg. Methylprednisolone depot is available for subconjunctival injection in

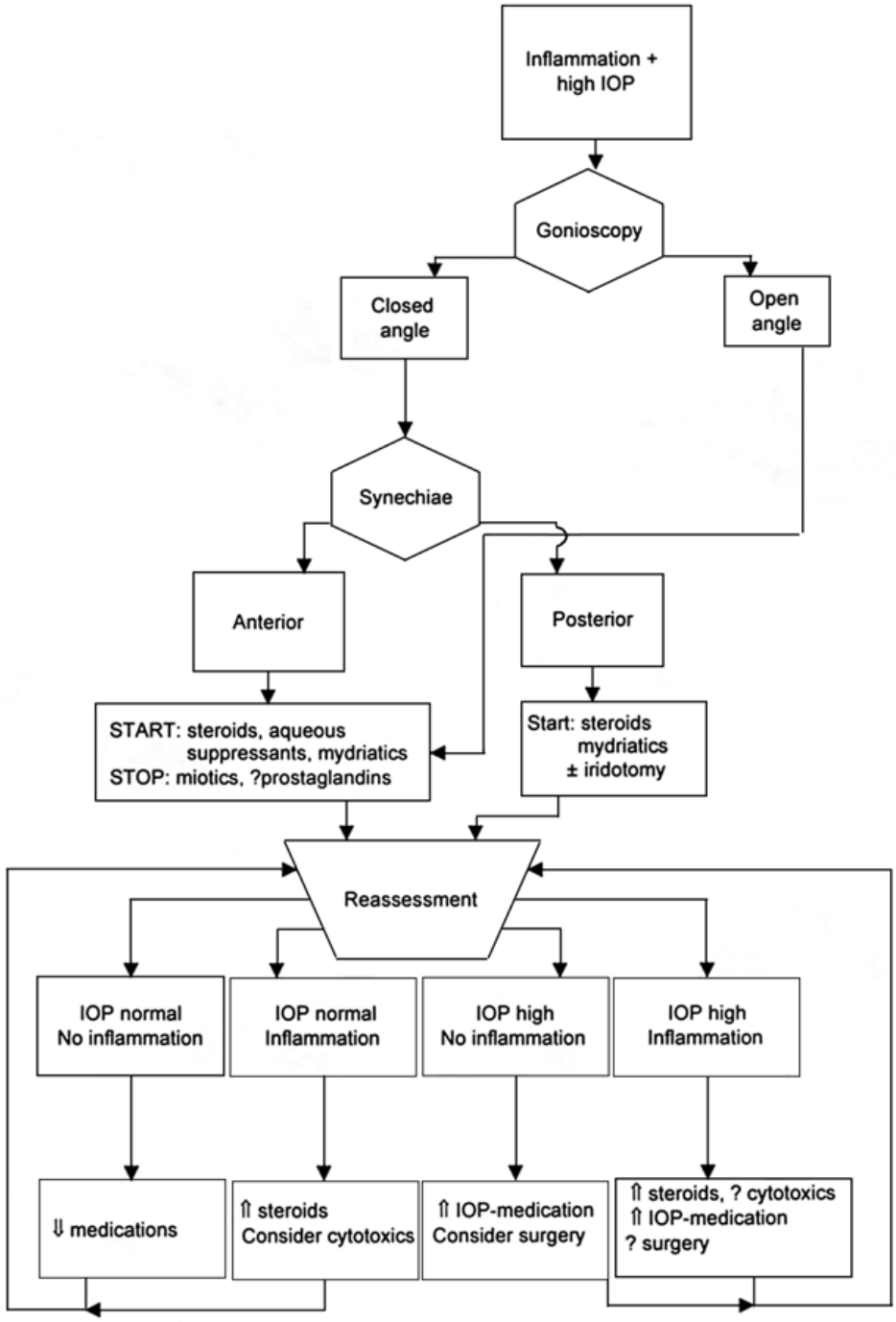

Figure 8–1. Management of uveitic glaucoma. IOP, intraocular pressure.

40 to 80 mg/0.5 mL concentrations. Triamcinolone suspensions are injected periocularly in 10- to 40-mg doses. Dexamethasone suspension may be injected with an initial dose of 2 to 4 mg. The blood–ocular barrier limits the intraocular penetration of systemic corticosteroids.[73]

Nonsteroidal Antiinflammatory Drugs

Therapy with NSAIDs is an important adjunct to application of topical, periocular, or systemic steroids. The amount of steroids and thus the rate of side effects can be significantly lessened with topical or oral use of NSAIDs.[83]

Mydriatic and Cycloplegic Agents

These agents are used to prevent posterior synechiae by dilating the pupil at regular intervals and thus keeping the pupil in motion. They also relieve ocular discomfort by relaxing the ciliary muscle. Homatropine 5% provides good mydriasis and adequate cycloplegia. Its duration of action is much shorter than that of atropine and scopolamine and will therefore keep the pupil much better in motion. Alternatively, a combination of tropicamide 1% and phenylephrine 2.5% can be given.[84] Cyclopentolate may be contraindicated in eyes with uveitis because it has been shown to be a chemoattractant to inflammatory cells in vitro.[85]

Aqueous Suppressants

Aqueous suppressants such as beta-blockers,[86] topical carbonic anhydrase inhibitors, and α^2-adrenergics are mainly used to lower the IOP in uveitic glaucoma. Carteolol was found to be effective for the treatment of secondary glaucoma associated with endogenous uveitis.[87]

What Medications and Procedures Should Be Avoided?

Miotics (parasympathetic drugs) should be avoided because they disrupt the blood–aqueous barrier and thus promote the intraocular inflammation.[88] Induced miosis would increase the surface area of the iris coming in contact with the lens, and thus may cause posterior synechiae and iris bombé. Concurrent ciliary body spasm may cause pain and blurred vision.

Prostaglandins such as latanoprost have been shown to cause anterior uveitis and therefore should probably be avoided in the treatment of uveitic glaucoma.[89] However, concurrent use of NSAIDs, such as diclofenac, might prevent disruption of the blood–aqueous barrier and maintain the IOP lowering effect.[90]

Caution should be exercised in patients with a history of glaucoma, previous surgery, or a predilection for uveitis when treated with Nd:YAG laser posterior capsulotomy. These patients may be at risk of developing ciliochoroidal effusions. Symptoms usually resolve after steroid treatment.[91]

Sympathetic uveitis may develop after filtering procedures on blind, painful eyes. It was the condition of the eye undergoing a filtering procedure that caused the sympathetic uveitis, and not the procedure itself. When glaucoma is

absolute, the risk is much higher. Filtering surgery on blind, painful eyes thus presents increased danger for the fellow eye.[92]

Is Immunosuppressive Therapy Useful?

Immunosuppression with antimetabolites (azathioprine, methotrexate), alkylators (cyclophosphamide, chlorambucil), and/or CsA is sometimes necessary to treat the ocular inflammation.[93,94]

What Is the Surgical Therapy?

Surgery should be avoided in an eye with active inflammation.[95] But when medical therapy fails, surgery is indicated. Iridoplasty, laser peripheral iridotomy, or peripheral iridectomy is recommended, when mydriatics fail to break posterior synechiae that are causing pupillary block. In cases of uncontrolled open- and closed-angle glaucoma, the following surgical options are available:

Filtering Surgery

Traditional filtering surgery has a low success rate in eyes with uveitic glaucoma. Failure of trabeculectomy most often results from fibroblast proliferation and subconjunctival fibrosis.[96] In patients with uveitis, excessive inflammatory response increases the risk of bleb failure.[97] Normal aqueous seems to inhibit subconjunctival fibroblast proliferation,[98,99] whereas aqueous[100–102] and conjunctiva[97] in uveitic eyes contain an increased number of T lymphocytes, which modulate wound healing. Success rates are higher when concurrent antiproliferative agents are used.[96,103,104]

Trabeculectomy with intraoperative application of mitomycin C for control of uveitic glaucoma achieved an IOP of 21 mm Hg or lower without glaucoma medications in 75%.[105]

Drainage Devices

Use of a drainage implant may be indicated as a primary procedure in glaucoma associated with uveitis.[106] Trabeculectomy was successful in four out of five eyes after 1 year, and in three out of four eyes after 2 years. Success rates for Molteno implants were defined as four out of five eyes in the same study and remained stable over 2 years. When significant inflammation is present, aqueous drainage devices are more likely to control IOP.[107]

Cyclodestructive Procedures

If medical and surgical therapy fail to control IOP, it may be necessary to ablate parts of the ciliary body to reduce aqueous inflow. Techniques for cyclodestruction that have been tried in the past include diathermy, electrolysis, and beta irradiation. Cyclocryotherapy is also available, although this technique has significant limitations. Newer techniques utilize laser energy (Nd:YAG or diode laser) via a transscleral approach. The disadvantages include the inability to precisely quantify the destruction of the ciliary processes and damage to adjacent

tissue. Transpupillary cyclophotocoagulation minimizes these problems, but is limited to the small number of eyes in which adequate gonioscopic visualization of the ciliary processes can be achieved. An alternative approach for aphakic eyes is intraocular cyclophotocoagulation, utilizing an endophotocoagulator through a pars plana incision. Depending on the status of the eye, visualization for this technique can be accomplished either by the transpupillary route or with an endoscope.[108] Cyclodestructive procedures need to be repeated more frequently when compared to drainage device procedures. However, patients with drainage devices are more likely to have other types of adverse ophthalmic events than patients who had a cyclodestructive procedure.[109]

Cyclodestructive therapy works best if the drainage angle is partially open. Postoperatively, increased inflammation, however, might close the angle further. It can cause phthisis bulbi more often than any other surgical procedure.

How Are Specific Uveitic Syndromes Handled?

Fuchs' Iridocyclitis

This is a syndrome that includes stellate keratic precipitates, heterochromia iridis, cataract, and a chronic anterior uveitis without anterior synechiae formation. The condition is typically unilateral. Fine blood vessels, which have a tendency to bleed very easily, but do not represent neovascularization, can be seen in the angle. Rubeosis iridis and rubeosis of the anterior chamber angle have also been reported.[110] Chronic anterior segment ischemia seen in Fuchs' heterochromic iridocyclitis can be possible mechanism predisposing these eyes to neovascularization.[111]

The prevalence of glaucoma in this condition varies from 6.3 to 59%.[57] The IOP is elevated secondary to reduced outflow facility. Glaucoma is usually treated with aqueous suppressants. The iritis does not respond well to corticosteroids, which by itself may induce IOP elevation in steroid responders. Most studies show that surgical intervention is required in approximately half of the patients;[112,113] 26.2% of patients with Fuchs' heterochromic uveitis had glaucoma. Half of these patients presented with glaucoma on initial examination. The risk of glaucoma in patients with Fuchs' heterochromic uveitis is 0.5% per year, decreasing significantly after 15 years. Causes of IOP elevation include inflammation with peripheral anterior synechiae, rubeosis, lens-induced angle closure, and recurrent spontaneous hyphema. Most patients have chronic open-angle glaucoma. Cataract surgery may precipitate glaucoma. The failure rate of glaucoma drainage surgery was 55.5%, and antimetabolites are needed for filtering surgery.[114]

Posner-Schlossman Syndrome (Glaucomatocyclitic Crisis)

This condition is usually unilateral.[115,116] Recurrent episodes of IOP elevation are usually asymptomatic. The angle remains open. The anterior chamber reaction is minimal. Corneal edema is usually present. Patients with Posner-Schlossman syndrome may have peptic ulcers and other gastrointestinal

disorders.[117] Usually individuals 20 to 50 years old are affected. This condition is self-limited and resolves spontaneously regardless of treatment. But aqueous suppressants and topical steroids may be indicated,[57] and patients rarely require filtering surgery.

Juvenile Rheumatoid Arthritis (JRA)

Juvenile rheumatoid arthritis is a general name for arthritic conditions in children and is relatively rare.[118] Secondary glaucoma is the most devastating complication of chronic uveitis[65] and can be seen in 14 to 27% of children.[119–123] The mechanism of glaucoma in JRA is either a pupillary block[95] and/or development of PAS with progressive angle closure.[118] Secondary open angle with obstruction of trabecular meshwork has been reported.[124] Because steroids are used in the treatment of JRA uveitis, steroid-induced glaucoma may occur. Medical management with topical and systemic aqueous suppressants initially controls IOP in about half of the patients, with only a third controlled later in the course of the disease.[125] Traditional filtering surgery is usually not very successful.[65,96,120] The use of antimetabolites with filtering surgery or shunting devices can improve the outcome.[57,64,105,107,126] In one study trabeculodialysis has been successful in more than half of the eyes after 2 years.[127]

Intermediate Uveitis (Pars Planitis)

Intermediate uveitis is defined as a clinical condition with usually bilateral inflammation of the peripheral retina ("snow banking") and vitritis.[128] It has been associated with sarcoidosis, multiple sclerosis, Lyme disease, and tuberculosis, but often remains idiopathic. Glaucoma occurs in 7 to 8% of adult patients with intermediate uveitis[60,129,130] and in 15% of children.[131,132] The IOP is elevated probably due to synechiae formation, rubeosis, and corticosteroid-induced glaucoma.[133]

Management includes topical aqueous suppressants. Cyclocryotherapy[131,134,135] has been used. Implantation of a drainage device might be necessary for uncontrolled glaucoma.

Behçet's Disease

This disorder presents with acute hypopyon, iritis, aphthous and genital ulcers, and erythema nodosum in young adults.[136,137] Ocular involvement is found in 83 to 95% in males and 67 to 73% in females; the male to female ratio is 1.78:1.[138]

Glaucoma usually occurs from obstruction of the trabecular meshwork by inflammatory cells and synechiae formation,[136] and sometimes neovascularization.[139–143] All patients initially respond to steroids, but steroids appear to be deleterious to visual prognosis and the patients eventually require cytotoxic-immunosuppressive drugs such as chlorambucil and cyclophosphamide after "resistance" to steroids develops. Glaucoma is treated with aqueous suppressants, filtration surgery, or drainage implants. The prognosis is poor. Only one of four patients had useful visual acuity after 10 years.[138,144]

Vogt-Koyanagi-Harada (VKH) Syndrome

Patients with VKH usually present with bilateral decreased vision and general symptoms such as headache, nausea, vomiting, and hearing loss. Bilateral panuveitis with serous retinal detachments and underlying choroidal infiltrates are seen. Perilimbal vitiligo is common.[145] Typically, affected individuals are 20 to 50 years of age and of Asian or Native-American descent. Uveitic glaucoma occurs in almost every third patient with VKH syndrome.[146–148] The IOP is usually elevated due to secondary open-angle glaucoma. Pupillary block due to posterior synechiae is also encountered frequently.[146–148] Rarely, angle closure secondary to choroidal effusion with anterior rotation of the ciliary body can be seen.[149] The main treatment consists of systemic corticosteroids. In severe cases or in patients who cannot tolerate high doses of steroids, cytotoxic agents or immunosuppressives such as CsA might be indicated.[147,150] The possibility of steroid-induced glaucoma must always be kept in mind. Glaucoma is treated medically with aqueous suppressants. If surgery is necessary, drainage devices offer a greater degree of success than trabeculectomies even with antiproliferative agents.[147,148]

Sympathetic Ophthalmia

This entity consists of bilateral granulomatous panuveitis after injury to one eye. Uveitic glaucoma develops in 43% of the eyes with sympathetic ophthalmia.[151] Filtering procedure on blind painful uveitic glaucoma eyes may provoke sympathetic ophthalmia in the fellow eye.[92] Mechanisms of uveitic glaucoma in sympathetic ophthalmia include angle closure secondary to pupillary block and iris bombé,[152] angle closure due to a thickening of the iris and ciliary body by cellular infiltration,[153] PAS and infiltration of the outflow pathway by inflammatory cells.[151] The main treatment for sympathetic ophthalmia consists of administration of topical and systemic corticosteroids and occasionally cytotoxic or immunosuppressive agents. Filtering surgery or implantation of a drainage device might be necessary.

Sarcoidosis

Ocular manifestations of sarcoidosis most commonly include bilateral chronic granulomatous uveitis with mutton fat keratic precipitates, iris nodules, and synechiae.[154] Ocular manifestations in systemic sarcoidosis occur in 38% of patients.[154] Granulomatous uveitis occurs in 52[154] to 74% of patients with ocular sarcoidosis. Glaucoma develops in 10.9 to 25.5% of patients with sarcoidosis uveitis.[154,155] Blacks with sarcoid uveitis have a higher risk than whites of developing glaucoma and blindness.[154]

Impairment to outflow in sarcoid uveitis arises from posterior and anterior synechiae, neovascularization of the angle and the iris, steroid-induced ocular hypertension,[156] and inflammatory precipitates and changes in the trabecular meshwork.[66] The aqueous level of angiotensin-converting enzyme (ACE) may be elevated in patients with uveitis suspected to have sarcoidosis and may need to be measured when serum ACE level and other laboratory and radiologic findings are negative.[157] Association of elevated serum levels of ACE in

patients with uveitis of unknown etiology suggests the diagnosis of ocular sarcoidosis.[158] Sarcoidosis can cause direct damage to the optic nerve and mimic glaucomatous optic neuropathy.[59] Glaucoma associated with sarcoid uveitis is treated with corticosteroids and aqueous suppressants. Filtering surgery or implantation of a drainage device is indicated if IOP cannot be medically controlled. Steroids should be used pre- and postoperatively. Pupillary block is treated with laser iridotomy or surgical iridectomy.

Herpetic Uveitis

Herpes Simplex Herpes simplex infection may present as superficial keratitis, disciform keratitis, necrotic stromal keratitis, neurotrophic ulcer, and retinitis. Approximately 5% of all uveitis cases in adults are associated with herpes simplex infection.[64] Increased IOP in ocular herpes infection associated with uveitis varies from 28 to 40%, but only 10% have secondary glaucoma.[6,64] Disciform and necrotic stromal keratitis is more commonly associated with increased IOP. In severe cases the incidence can reach 80%.[6] Obstruction of the trabecular meshwork with inflammatory products, trabeculitis,[6,13] and angle closure[71] most commonly cause IOP elevation in herpetic uveitis. The initial management of elevated IOP is directed at controlling viral replication. Oral and/or topical acyclovir and topical trifluridine are most effective because they penetrate the ocular tissues easily. Topical cycloplegics are helpful to control ciliary spasm, and topical corticosteroids may be used if inflammation is severe or persists despite the antiviral treatment. Topical steroids alone can reactivate or aggravate the herpetic infection. Therefore, they should never be used without initial antiviral coverage. IOP usually returns to normal levels when the inflammation subsides. Aqueous suppressants are effective if IOP needs to be controlled. About 10% of patients who have persistent IOP elevation despite medical treatment may require surgery.[6]

Herpes Zoster Ocular involvement occurs in two-thirds of patients with herpes zoster ophthalmicus. This might include conjunctivitis, superficial keratitis, stromal keratitis, neurotrophic keratitis, uveitis, scleritis, retinitis, choroiditis, and optic neuritis. Elevation of IOP and glaucoma occurs in 16 to 50% of cases associated with corneal involvement of keratitis and uveitis.[17,64,159] Decreased outflow facility due to trabeculitis and inflammatory debris in the trabecular meshwork is thought to cause the IOP elevation.[160,161]

Oral acyclovir given early in the course of the disease seems to reduce the risk of complications, such as uveitis and associated elevated IOP.[162] Later in the course of the disease, uveitis is no longer due to viral replication, but rather to ischemia.[163] Uveitis and IOP should then be treated with topical corticosteroids, mydriatics, and aqueous suppressants as indicated.

Future Considerations

Mycophenolate mofetil (MMF), a potent selective uncompetitive and reversible inhibitor of ionisine monophosphate dehydrogenase involved in purine synthesis is currently under investigation. It is an immunosuppressive and

steroid-sparing agent, which can be used to treat ocular inflammatory disease. In a recent study mycophenolate mofetil was given 1 g twice daily in conjunction with steroids, as a steroid-sparing agent, or as an additional agent with CsA, or instead of CsA or azathioprine.[164] The addition of MMF to immunosuppressive regimens improved symptoms and allowed reducing the dose of prednisone in most patients. MMF may become a useful immunosuppressive drug for controlling ocular inflammation without significant side effects.

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Pigmentary Glaucoma

Jess T. Whitson

Definition of the Problem

What Is Pigmentary Glaucoma?

Pigmentary glaucoma is a form of secondary open-angle glaucoma, which is characterized by the presence of radial midperipheral iris transillumination defects, pigment deposition on the corneal endothelium (Krukenberg's spindle), and dense pigmentation of the trabecular meshwork. When these slit-lamp findings are present without elevated intraocular pressure (IOP), the condition is known as pigment dispersion syndrome.

When Was Pigmentary Glaucoma First Described?

Krukenberg[1] initially described the vertical, central pigment deposition on the corneal endothelium, which now bears his name, in 1899. Later authors such as Von Hippel[2] and Jess[3] hypothesized that pigment dispersion may contribute to elevated IOP in glaucoma patients. The term *pigmentary glaucoma* was first used in the 1940s when Sugar and Barbour[4] described two myopic glaucoma patients with excessive pigmentation of the trabecular meshwork. Later authors identified the source of this pigment as the neuroepithelium along the posterior surface of the iris, accounting for the characteristic transillumination defects.[5,6]

Epidemiology and Importance

Who Is at Risk for Pigmentary Glaucoma?

Pigmentary glaucoma typically occurs in young adults. Although pigment dispersion syndrome is as common or more common in women than men,

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pigmentary glaucoma is typically found in men.[7, 8] Moreover, the development of glaucoma is usually earlier in men, with an average age of onset of 34 to 46 years, compared to women, who have an average age of onset of 46 to 53 years.[7,8] The most common refractive error seen in pigmentary glaucoma is mild to moderate myopia.[8] Berger and associates[9] reported that higher degrees of myopia may lead to an earlier age of onset of glaucomatous optic nerve damage in patients with pigmentary glaucoma.

Although pigmentary glaucoma is characteristically found in whites, it has also been reported in a black albino patient[10] and a mulatto family.[8] In their large review of the risk factors for the development and severity of glaucoma in the pigment dispersion syndrome, Farrar et al[11] examined the medical records of 93 patients with pigmentary glaucoma and 18 patients with pigment dispersion syndrome. They identified male gender, black race, severe myopia, and presence of Krukenberg's spindle as possible risk factors for the presence of secondary glaucoma. Men made up two-thirds of this population and developed glaucoma at an earlier age requiring more extensive therapy. Although only four black patients were found in this study, they displayed a particularly aggressive form of the disease and all required surgical intervention.

Although pigmentary glaucoma typically occurs in young adults, it may also be found in older patients as well. Because the clinical manifestations of the disorder may diminish with time, older patients may present with normalized IOP and regressed pigmentary changes, but showing optic nerve damage, leading to an erroneous diagnosis of normal tension glaucoma.[12]

What Are the Genetic Characteristics of Patients?

Our understanding of the genetics of pigmentary glaucoma continues to unfold. Although many cases of pigmentary glaucoma and pigmentary dispersion syndrome are sporadic, an early report by Stankovic[13] suggested an autosomal recessive pattern of inheritance for the disorder. A more recent article by Olander and co-workers[14] supports transmission by either an autosomal dominant or recessive pattern. Support for a genetic basis for the disease comes from its observation in siblings and twins, and the fact that there is an increased incidence of open-angle glaucoma in the families of patients with pigment dispersion syndrome. Pigment dispersion patients also show an increased incidence of steroid responsiveness, indicating a possible underlying predisposition for open-angle glaucoma. Andersen and associates[15] studied 54 members of four families with pigment dispersion syndrome and pigmentary glaucoma. Twenty-eight patients showed clinical evidence of the pigment dispersion syndrome, of whom 14 required medical or surgical treatment. These authors found the pigment dispersion syndrome to be inherited as an autosomal dominant trait in these four families, and they linked the gene responsible for the syndrome to the telomeric end of the long arm of chromosome 7q35-q36. Although still very early in development, the isolation and characterization of the gene responsible for pigment dispersion syndrome may someday help us better understand the pathophysiology of the disorder and lead to new methods of diagnosis and treatment.

How Common Are the Pigment Dispersion Syndrome and Pigmentary Glaucoma?

The pigment dispersion syndrome has been found to be much more common than was originally reported.[4] Ritch and associates[16] performed two large population screenings, which included slit-lamp examination, and detected pigment dispersion syndrome in 18 of 934 individuals for an overall prevalence of 1.93%, and 2.45% of white patients. The authors noted that many of these patients displayed a very mild form of the syndrome and concluded that many similar patients probably go undetected in their lifetime. Likewise, pigmentary glaucoma is not uncommon as well, and may account for up to 1.5% of all glaucomas worldwide.[17]

The percentage of patients with pigment dispersion syndrome who develop pigmentary glaucoma is unclear. An early report by Wilensky and co-workers[18] found that only two of 43 patients who presented with Krukenberg's spindle and normal visual fields developed visual field loss after 5.8 years. More recent longitudinal studies, however, have suggested that up to 50% of patients with pigment dispersion may eventually develop pigmentary glaucoma.[11,19,20] Migliazzo and associates[19] reported a retrospective, longitudinal review of 129 eyes in 65 patients with pigment dispersion syndrome. Visual acuity, IOP, visual field loss, pigment grade, Krukenberg's spindle, iris transillumination defects, medications, and surgeries were analyzed for each patient at 5-year intervals for an average follow-up period of 17 years. Optic disc and visual field changes developed in 35% of patients with pigment dispersion and ocular hypertension during the study period. Richter and co-workers[20] performed a prospective study of the natural history of pigment dispersion syndrome and pigmentary glaucoma in 55 patients for an average follow-up of 27 months. They observed active pigment dispersion, defined by increase in iris transillumination or corneal pigmentation or by the appearance of pigment granules on the surface of the lens, in 45 eyes of 31 patients and was associated with worsening of glaucoma in 32 eyes. They found no differences in the frequency of active dispersion of pigment and worsening of glaucoma with respect to age, even in those patients older than 65 years. The authors concluded that progression of pigmentary glaucoma is correlated with active pigment dispersion and may continue to occur in older patients.

Other risk factors for the development of glaucoma in pigment dispersion patients include male gender, severe myopia, and presence of Krukenberg's spindles[11] (Table 9–1). Once present, pigmentary glaucoma may be more difficult to control than primary open-angle glaucoma (POAG). In a large series, Scheie and Cameron[8] found surgical intervention was required in 23.5% of pigmentary glaucoma patients compared with 14.6% of patients with POAG.

Table 9–1. Risk Factors for Pigmentary Glaucoma

Male gender
White race
Young age (3d to 4th decade of life)
Mild to moderate myopia

Diagnosis and Differential Diagnosis

What Are the Clinical Features of Pigmentary Glaucoma?

Pigmentary glaucoma and the pigment dispersion syndrome are characterized by a central vertical deposition of pigment along the corneal endothelium. Aqueous convection currents from the nasal and temporal halves of the anterior chamber result in the typical distribution pattern, with more pigment collecting inferiorly than superiorly. The endothelial cells phagocytose the pigment and apparently maintain their normal function, as normal endothelial cell counts and corneal thicknesses have been reported in pigment dispersion syndrome.[21] Pigment may also accumulate along the anterior iris surface, leading to the development of heterochromia in cases of asymmetric pigment dispersion.[22] Midperipheral iris transillumination defects, seen by scleral transillumination or retroillumination at the slit lamp, are characteristic findings in pigmentary glaucoma. The defects, which correspond in location to the underlying anterior lens zonules, may vary in severity from a few spoke-like changes to 360-degree involvement of the iris.

Pigment may be deposited on the posterior lens capsule and tends to collect in a ring corresponding to the location of the attachment of the zonules. This "Scheie's line" is considered to be pathognomonic for pigment dispersion syndrome.[23] Individual pigment particles may also be seen on the anterior lens capsule and anterior zonules.[20]

Pigment also collects in the angle structures, especially within the trabecular meshwork. This is seen gonioscopically as a heavy, dark discoloration over its entire circumference. A pigmented Schwalbe's line, or Sampaolesis' line, is also typically seen. Several authors have described an increased number of iris processes in patients with pigmentary glaucoma.[24,25] The ciliary band is typically seen easily on gonioscopy as expected in a large, myopic eye. Clinical features of pigment dispersion syndrome and pigmentary glaucoma are listed in Table 9–2.

How Do Exercise and Pupillary Dilation Affect Pigmentary Glaucoma Patients?

Patients with pigment dispersion syndrome or pigmentary glaucoma may shed excess pigment following exercise[26] or pupillary dilation,[27] with a resul-

Table 9-2. Clinical Features of Pigmentary Glaucoma

Pigment dispersion syndrome
Krukenberg's spindle
Midperipheral iris transillumination defects
Excess pigmentation of the angle
Pigmentary glaucoma
All of the above, plus:
Elevated intraocular pressure
Glaucomatous optic disc atrophy
Characteristic visual field changes

tant increase in IOP. This induced pigment release and IOP elevation can be blocked by pilocarpine[28] and partially blocked by laser iridotomy.[29] Shenker and associates[26] describe a 32-year-old white man with pigment dispersion syndrome who developed a significant rise in IOP and anterior chamber pigment release shortly after playing basketball. The authors concluded that active pigment dispersion caused by exercise led to an acute rise in IOP.

Exercise, however, does not always lead to an increase in IOP in pigmentary glaucoma patients. Smith and co-workers[30] measured IOP in 10 pigmentary glaucoma patients following a 25-minute exercise protocol. Applanation tonometry measurements during the first 2 hours after exercise showed no statistically significant rise in IOP in any of the patients. Other authors have reported a decrease in IOP in pigmentary glaucoma patients following exercise.[31] The mechanism for decreased IOP following exercise is not clear, although some authors have suggested increased plasma osmolarity[32] or increased facility of outflow[33] as possible mechanisms. Although exercise may not elevate IOP in all pigmentary glaucoma patients, those who complain of blurring vision or halos around lights following vigorous activity should be checked to see what, if any, IOP response they may have.

What Is the Pathophysiology of Pigment Dispersion Syndrome?

Initially, loss of iris pigment was thought to be congenital in origin, resulting from either the maldevelopment of the pigment layer with resultant atrophy[34] or cellular hyperplasia of the muscular portion of the iris neuroepithelium.[35] This hereditary developmental concept has been supported by the association of pigmentary glaucoma with abnormalities of the retinal pigment epithelium and peripheral retina.[36,37] In 1979, Campbell[38] described a new mechanism for pigment dispersion after noting the high prevalence of posterior iris bowing in pigmentary glaucoma patients. He proposed that friction between the posterior iris surface and underlying lens zonules, which occurs during normal pupillary movement, damages the epithelial cells and results in pigment release. This theory was later confirmed by Kampik and associates[39] using scanning and transmission electron microscopy.

A reverse pupillary block mechanism in which the iris acts as a "flap valve" to maintain a pressure gradient between the anterior and posterior chambers was described by Karickhoff.[40] In this hypothesis, the iris is pushed backward against the anterior lens zonules when a higher pressure exists in the anterior as compared to the posterior chamber of the eye. The reverse pupillary block mechanism has been well demonstrated by ultrasound biomicroscopy[41] and can be relieved by laser iridotomy,[29] with resultant iris flattening and loss of iridolenticular contact.

Several theories for the development of reverse pupillary block have been proposed. Campbell[42] and Liebmann et al[43] have shown that cessation of blinking in patients with concave irides results in iris flattening. This led them to propose that normal blinking may produce transient vector forces within the eye, causing aqueous to flow from the posterior to the anterior chamber. The iris then acts as a flap valve as described by Karickhoff[40] to maintain a pressure gradient between the two chambers. The higher pressure in the anterior chamber

then pushes the iris posteriorly, creating a reverse pupillary block. Pavlin and coworkers[44] have shown that accommodation can increase iris concavity in some patients with pigment dispersion syndrome, most likely through an accommodation-induced relative increase in anterior chamber pressure secondary to forward movement of the lens surface. They found that laser iridotomy could be used to prevent these changes in iris configuration seen with accommodation. Finally, exercise may augment posterior iris bowing, possibly through a heightened ocular pulse, which may increase cyclic aqueous movements through the pupil.[45] As with accommodation, the posterior iris bowing that occurs with exercise in these patients can be eliminated by laser iridotomy.

What Is the Clinical Course of Pigmentary Glaucoma?

The onset of pigment dispersion syndrome is thought to occur in most patients during the third decade of life. An active phase of pigment dispersion, which may last for many years, is typically followed by a regression phase, during which pigment liberation is markedly reduced or ceases completely. During this later phase, decreasing corneal endothelial pigment, a reduction in the number of iris transillumination defects,[38] and normalization of IOP[46] are often seen clinically. Older patients may be left with only a pigment reversal sign, in which the normal pattern of pigmentation reverses, becoming darker superiorly than inferiorly, suggesting a previous history of pigment dispersion.[47]

Studies have shown that most patients with pigment dispersion syndrome do not develop increased IOP and optic nerve damage.[11,19,20] Richter and associates[20] reported that in most patients with pigmentary glaucoma, active pigment dispersion was associated with elevated IOP and progression of glaucomatous nerve damage. Küchle and co-workers[48] have recently developed a technique using the laser flare-cell meter to quantify aqueous melanin granules in pigmentary glaucoma patients, which may prove useful in evaluating eyes with pigment dispersion syndrome and assessing treatment efficacy.

What Causes Elevated IOP in Pigmentary Glaucoma Patients?

Richardson et al[49] have shown that in eyes with pigmentary glaucoma, trabecular meshwork cells phagocytose dispersed pigment particles and then disintegrate or migrate away from the trabecular beams. This response is typically accompanied by localized collapse of the trabecular meshwork, with resultant decreased aqueous outflow facility. In patients with pigment dispersion syndrome, however, the intertrabecular spaces remain open and, except for the presence of pigment-laden epithelial cells, meshwork architecture remains intact. Campbell and co-workers[50] performed perfusion studies on rhesus monkey eyes and found that fewer particles could produce an acute rise in IOP than would be expected with intertrabecular obstruction alone. Histologic studies on those monkeys with acute IOP elevation from pigment perfusion showed features similar to those seen in POAG, such as collapse of intertrabecular spaces associated with obstruction by debris.[50] From these results the authors concluded that trabecular meshwork damage in pigmentary glaucoma arises from some other mechanism in addition to intertrabecular obstruction.

What Is the Differential Diagnosis of Pigmentary Glaucoma?

The differential diagnosis of pigmentary glaucoma is listed in Table 9–3. Patients with pseudoexfoliation syndrome typically develop peripupillary iris atrophy in contrast to the midperipheral iris transillumination defects seen exclusively in pigment dispersion syndrome and pigmentary glaucoma. Although small amounts of pigment may collect on the corneal endothelium in pseudoexfoliation syndrome, a typical Krukenberg's spindle does not develop. The trabecular pigmentation in pseudoexfoliation syndrome is patchy and irregular as opposed to the dense homogeneous band found in pigmentary glaucoma. Finally, pigmentary glaucoma patients lack the typical collection of pseudoexfoliative material on the anterior lens capsule seen in pseudoexfoliation syndrome.

Pigmentary glaucoma can be readily distinguished from uveitis by its lack of other signs of inflammation such as the formation of posterior or peripheral anterior synechiae and keratic precipitates. Ocular melanosis (congenital melanosis oculi) is typically unilateral and consists of abnormal pigmentation in the sclera, episclera, and uveal tissue. Signs of pigmentary glaucoma are absent. Placement of a posterior chamber intraocular lens in the ciliary sulcus rather than the capsular bag following cataract extraction may result in chronic iris chafing by the lens haptics with pigment liberation and secondary glaucoma.[51]

Unilateral pigmentary dispersion syndrome with secondary glaucoma is typically seen in association with an iris or ciliary body cyst or melanoma. Rarely, iris ring melanoma may masquerade as unilateral pigmentary glaucoma.[52] Other signs of pigmentary glaucoma, such as transillumination defects or Krukenberg's spindles, are typically absent in these patients, whereas the cyst or tumor can often be found easily during gonioscopy or on dilated examination. Unilateral pigment dispersion with secondary glaucoma may also be seen with angle recession.[53] Evidence on gonioscopy or history of ocular trauma is typically present. The decision tree for the differential diagnosis of patients with pigmentary glaucoma is shown in Figure 9–1.

What Retinal Disorders May Be Associated with Pigmentary Glaucoma?

Retinal abnormalities have been reported in patients with pigment dispersion syndrome and pigmentary glaucoma (Table 9–4). Chew and Deutman[36] initially described retinal pigment epithelial (RPE) changes in the posterior pole of a patient with pigment dispersion syndrome. Fluorescein angiography showed a "fishnet" pattern typical of pigmented pattern dystrophy of the RPE.

Table 9-3. Differential Diagnosis of Pigmentary Glaucoma

Pseudoexfoliation syndrome
Uveitis
Ocular melanosis
Pseudophakic pigment dispersion
Intraocular cyst or tumor
Angle recession with pigment dispersion

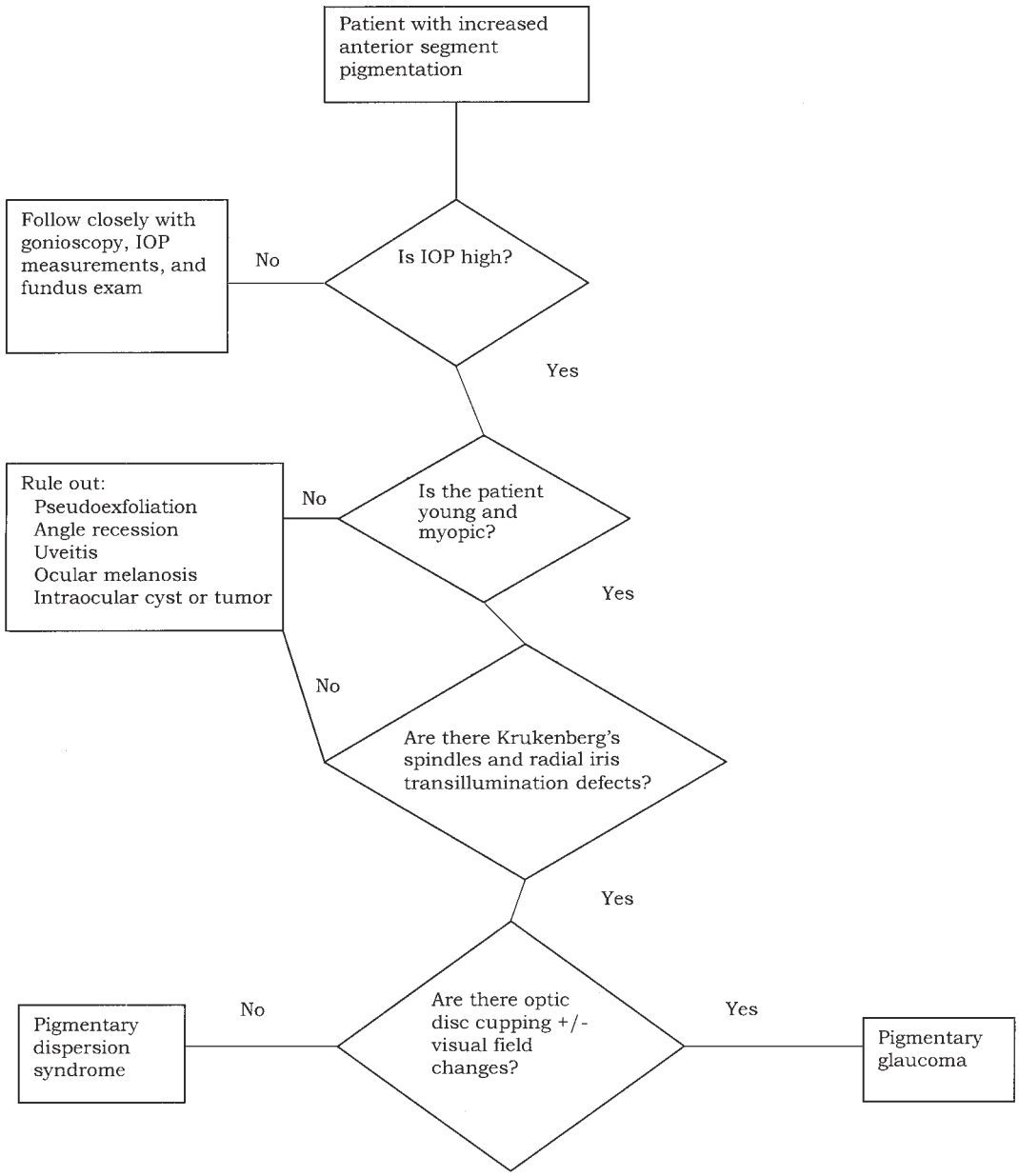

Figure 9-1. Differential diagnosis of patient with pigmentary glaucoma.

Cardillo Piccolino and associates[37] later described two brothers with pigmentary glaucoma who presented with bilateral degeneration of the peripapillary RPE, one of whom developed recurrent serous RPE detachments and neovascular choroidal membranes. Weseley and co-workers[54] reported an incidence of lattice degeneration of the peripheral retina of 16.0% in 119 pigment dispersion patients. Scuderi and co-workers[55] found lattice degeneration to be present in 33.3% of 24 patients with pigment dispersion. The authors accounted

Table 9-4. Retinal Abnormalities Associated with Pigmentary Glaucoma

Degeneration of the retinal pigment epithelium
Lattice degeneration
Increased risk of rhegmatogenous retinal detachment

for the higher incidence of lattice degeneration in their series compared to that of Weseley et al[14] by noting that the mean age of their study group was approximately 10 years higher than Weseley's and that their patients were less myopic and thus less likely to exhibit lattice degeneration, which is more common in patients with myopia of 3.00 diopter (D) or less.[56] Weakness of the peripheral retina was also noted by Brachet and Chermet,[57] who reported 19 cases of rhegmatogenous retinal detachment in pigmentary dispersion patients. Finally, Scheie and Cameron[8] found an incidence of retinal detachment of 6.6% in pigment dispersion patients and 7.6% in pigmentary glaucoma patients. This is much higher than the expected annual incidence of phakic, nontraumatic retinal detachment in the general population, which has been reported to be 0.005% to 0.01%. Furthermore, the majority of patients with retinal detachments in Scheie and Cameron's series were only moderately myopic, suggesting that the increased risk for retinal detachment in pigment dispersion syndrome is substantial.

Treatment and Management

What Is the Treatment for Pigmentary Glaucoma?

The treatment for pigmentary glaucoma is similar to that for POAG (Table 9–5). Often with mild IOP elevation and optic disc damage, a topical beta-blocker is sufficient to lower IOP and prevent further visual field loss. When IOP remains elevated or evidence of visual field progression develops, other aqueous suppressants, such as α_2-agonists or carbonic anhydrase inhibitors, may be added.

Table 9-5. Treatment of Pigmentary Glaucoma

Aqueous suppressants
Beta-blockers
α_2-agonists
Carbonic anhydrase inhibitors
Increased aqueous outflow
Prostaglandin $F_{2\alpha}$
Miotics
Pilocarpine
Carbachol
Dapiprazole
Argon laser trabeculoplasty
Laser iridotomy
Filtration surgery

Because the conventional aqueous outflow pathway is compromised in pigmentary glaucoma, drugs that increase outflow through the uveoscleral pathway, such as prostaglandin $F_{2\alpha}$, may have added beneficial effect.

In some patients, the addition of a miotic, such as pilocarpine or carbachol, may be necessary. Along with increasing aqueous outflow, miotics may help prevent progression of the disease by flattening the iris and preventing further iridozonular contact and pigment dispersion.[28] Unfortunately, miotic therapy is often poorly tolerated in young myopic patients because of accommodative spasm and increased myopia. In these patients, sustained-release forms of the drug, such as pilocarpine gel or Ocuserts, can sometimes be used more effectively. Miotics should be used cautiously in these patients and only after a dilated retinal exam, because of the association of peripheral retinal pathology and pigmentary glaucoma.[57] Because of their ability to produce miosis and iris flattening without ciliary spasm and induced myopia, α-adrenergic antagonists, such as thymoxamine, may someday play an important role in the treatment of pigmentary glaucoma. Mastropasqua and associates[58] have shown that long-term therapy with dapiprazole, an α-adrenergic antagonist, results in significantly increased outflow facility in pigmentary glaucoma patients. The disadvantages of dapiprazole include high cost of the medication and short shelf-life after reconstituting.

For those patients who are not adequately controlled with medical therapy, argon laser trabeculoplasty (ALT) can sometimes be used successfully, especially in younger patients, although its effect is usually short-lived. Lunde[59] reported that an initial drop of 10.6 mm Hg following ALT in 13 eyes of 10 patients with pigmentary glaucoma was followed by an increase in IOP to higher than baseline levels after 9 months. Lehto[60] reported an initial IOP-lowering effect of 53% in pigmentary glaucoma patients, which decreased to only 14% after 3 months. When performing ALT in pigmentary glaucoma patients, lower energy levels should be used because of the increased pigmentation and energy absorption of the trabecular meshwork.

Peripheral iridotomy has been shown to alleviate the reverse papillary block and iris concavity seen in pigment dispersion patients, thus preventing iridozonular contact and further pigment dispersion. Gandolfi and Vecchi[61] found a markedly reduced incidence of ocular hypertension in eyes with pigment dispersion syndrome following laser iridotomy. At this point, the role that laser iridotomy may play in the management of pigment dispersion syndrome and pigmentary glaucoma requires further study.

Filtration surgery is necessary in those patients who fail medical and laser therapy. Scheie and Cameron[8] found that pigmentary glaucoma patients more frequently required surgical intervention than patients with POAG. Success rates of filtration surgery for these two groups of patients are similar.

Future Considerations

Where Is the Research on Pigmentary Glaucoma Heading?

Much has been learned about pigmentary glaucoma since its original description by Sugar and Barbour[4] in the 1940s. Once thought to be a rare disorder, it

is now known to be fairly common, with a prevalence of 2.45% in a large screening population.[16] Future considerations for the diagnosis and treatment of pigment dispersion syndrome and pigmentary glaucoma appear quite promising. The α-adrenergic antagonists such as dapiprazole and thymoxamine, which produce miosis and iris flattening with increased aqueous outflow facility and without the induced myopia and ciliary spasm of pilocarpine, are promising. α-adrenergic antagonists, however, are not yet available for clinical use in the United States. Peripheral iridotomy, with its ability to alleviate the reverse pupillary block mechanism described by Karickhoff[40] may also become more important in the treatment of the disorder, especially early in its course. New methods of patient evaluation, such as the technique for quantification of aqueous melanin granules as described by Küchle and associates[48] may help us better assess treatment efficacy. Finally, gene therapy may someday play a role in the disorder as we build on the work of Andersen et al[15] and better characterize the genetic basis of pigment dispersion syndrome.

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◆ 10 ◆

Glaucoma Associated with Lens Disorders

Gustavo E. Gamero

Definition

This chapter discusses glaucoma as a direct or indirect result of some lens abnormality. A careful assessment of this heterogeneous group of diseases will result in the selection of the appropriate management. This discussion does not include cases in which glaucoma and the lens pathology simply coexist and a cause-effect relationship is not present.[1, 2]

How Is Glaucoma Associated with Lens Disorders Classified?

From a practical viewpoint these entities can be initially approached according to broad clinical features and then subdivided into more specific patterns of disease. We group together entities that have similarities either in their clinical picture or pathogenic mechanism. Accordingly, these glaucomas may be divided into four major categories: (1) glaucoma associated with ectopia lentis, (2) glaucoma associated with cataract, (3) glaucoma associated with exfoliation syndrome, and (4) glaucoma associated with aphakia and pseudophakia.

Frequent overlapping of clinical features and mechanisms of disease is commonly seen.[2] As a result some clinical presentations fit more than one disease category. For example, an eye with phacolytic glaucoma may also have a dislocated lens and angle recession from prior trauma. It is understood that not all possibilities can be outlined separately, and more than one decision-making route may be needed to reach the proper diagnosis. Complex diseases are to be evaluated on a case-by-case basis. By using an approach based on questions and answers, this chapter guides the reader through the appropriate differential diagnosis to select the correct treatment.

Clinical Pathways in Glaucoma. Edited by Zimmerman and Kooner.
Thieme Medical Publishers, Inc., New York © 2001.

Epidemiology and Importance

This is a very heterogeneous group of diseases that includes distinct hereditary and nonhereditary conditions. As a group they represent a small percentage of the total number of patients with glaucoma, but their impact on the health of the eye can be devastating if treatment is not instituted promptly.[1] These patients usually present to ophthalmology clinics with a specific problem. With the exception of exfoliation syndrome, they are not the usual subjects for major population glaucoma studies. In general, the glaucoma associated with hereditary syndromes (e.g., homocystinuria, Weill-Marchesani syndrome) tends to present at an earlier age as the inborn lens abnormality progresses.[2] These syndromes do not show a predilection for race or ethnic group and occur as a result of specific chromosomal abnormalities. Other entities, such as glaucomas associated with cataract or exfoliation syndrome, characteristically present in the elderly with variable severity. The presence of cataracts clearly increases with age,[3] whereas the presence of exfoliation does show a predilection for certain ethnic backgrounds (see Glaucoma Associated with Exfoliation Syndrome, below).

GLAUCOMA ASSOCIATED WITH ECTOPIA LENTIS

Definition

What Is Glaucoma Associated with Ectopia Lentis?

This type of glaucoma is caused primarily by the abnormal position of the lens and its consequences.[3] The various clinical conditions associated with ectopia lentis are listed in Table 10–1. Concurrent factors such as angle abnormalities or vitreous prolapse may play additional roles in the pathogenesis of the glaucoma.[4]

Table 10–1. Entities Commonly Associated with Ectopia Lentis[a]

Isolated ectopia lentis
Simple ectopia lentis
Ectopia lentis et pupillae
Systemic disorders
Marfan syndrome*
Homocystinuria*
Weill-Marchesani syndrome*
Hyperlysinemia
Sulfite oxidase deficiency
Ocular disorders
Trauma
Aniridia
Megalocornea
Others**

[a]Entities only rarely associated with ectopia lentis are not considered in this list.
*These entities make up more than 95% of the cases of nontraumatic, bilateral ectopia lentis.
**Less common entities include congenital glaucoma, high myopia, Ehlers-Danlos syndrome, hyperlysinemia, syphilis.

Epidemiology and Importance

Congenital ectopia lentis is a rare condition, and Marfan syndrome, homocystinuria, and Weill-Marchesani syndrome represent more than 95% of cases. Marfan syndrome has a prevalence of 4 to 6 per 100,000,[5] with 60 to 80% developing ectopia lentis. Homocystinuria is even more rare, having a frequency of 0.021% in the mentally retarded,[5] with 90% developing ectopia lentis. Weill-Marchesani is more rare than Marfan and homocystinuria, and 80 to 90% of these patients develops ectopia lentis. Epidemiologic data on specific acquired conditions such as exfoliation syndrome will be mentioned when the pertinent entities are discussed.

Diagnosis and Differential Diagnosis

What Is the Pathogenesis of Glaucoma in Ectopia Lentis?

The following basic mechanisms of disease apply to most types of ectopia lentis (see Table 10–2). In general open-angle and angle-closure mechanisms can take place. Open-angle glaucoma has been divided in pretrabecular (usually membranes occluding the trabecular meshwork at the angle), trabecular (idiopathic and trabecular blockage by abnormal elements or distortion) and posttrabecular (Schlemm's canal damage or elevated episcleral venous pressure). Angle closure can be caused by anterior ("pulling") and posterior ("pushing") forces, resulting in iris apposition to the cornea.[1] Some specific differences will be pointed out when the pertinent entity is discussed.

Open-angle mechanisms consist of structural angle abnormalities and can contribute to the glaucoma in some syndromes.[5] Pupillary-block angle closure is the most common mechanism and results from anterior displacement of the lens toward the pupil.[2] The clinical presentation varies according to the degree and acuteness of the pupillary block. Therefore, acute, subacute, and chronic angle-closure glaucoma can occur. Vitreous prolapse around the dislocated lens can play an additional role in blocking the pupil and in some cases be the main factor.[4] Total dislocation of the lens into the anterior chamber can occlude the pupil anteriorly causing an acute rise in intraocular pressure (IOP) (Tables 10–2 and 10–3). Finally, concurrent processes other than lens dislocation can contribute to the pathogenesis of glaucoma, such as trauma, hemorrhage, neovascularization, and cataract.

How Is Glaucoma in Ectopia Lentis Diagnosed?

The diagnosis of ectopia lentis begins with a good history and physical examination. A complete eye examination must be performed including a slit-lamp evaluation before and after maximal pupillary dilatation. After an initial external examination, a complete systemic workup is done to detect potentially serious conditions associated with ectopia lentis.[5] The most noticeable conditions are cardiovascular complications in Marfan syndrome, and thromboembolic disease in homocystinuria (see below). Once a sustained elevation of IOP is documented, the diagnosis of ectopia lentis and glaucoma is made and the differential diagnosis can be outlined.

Table 10–2. Possible Mechanisms of Glaucoma in Ectopia Lentis

Open-angle mechanisms
Pretrabecular
Phacolytic
Exfoliative
Inflammatory elements
Trabecular
Trabecular trauma
Trabecular inflammation
Congenital anomaly*
Angle-closure mechanisms
Anterior type ("pulling")
PAS from trauma
PAS from inflammation
Posterior type ("pushing")
Pupillary block*
Phacomorphic

PAS, peripheral anterior synechiae.
*These mechanisms present with "pure" ectopia lentis. The other mechanisms imply the presence of concurrent ocular conditions.

What Is the Differential Diagnosis of Glaucoma with Ectopia Lentis?

The list of all conditions associated with ectopia lentis is a long one;[4] the most common ones are listed in Table 10–1. The differential diagnosis addresses the most common entities associated with glaucoma (Fig. 10–1).

Is There a History of Ocular Trauma?

The history of ocular trauma should be specifically sought, especially in cases of unilateral ectopia lentis and glaucoma. For a discussion of glaucoma associated with trauma see Chapter 13.

Table 10–3. Ectopia Lentis, Glaucoma, and Congenital Syndromes

Feature		Marfan Syndrome	Homocystinuria	Weill-Marchesani Syndrome
Prevalence of ectopia lentis		60–80%	90%	80–90%
Prevalence of glaucoma		8%	25%	75%
Anterior dislocation		+	+ + +	+ + +
Angle abnormalities		+ +	–	+
Mechanism of the glaucoma	Pupillary block	+ + +	+ + +	+ + +
	Angle abnormality	+	–	+

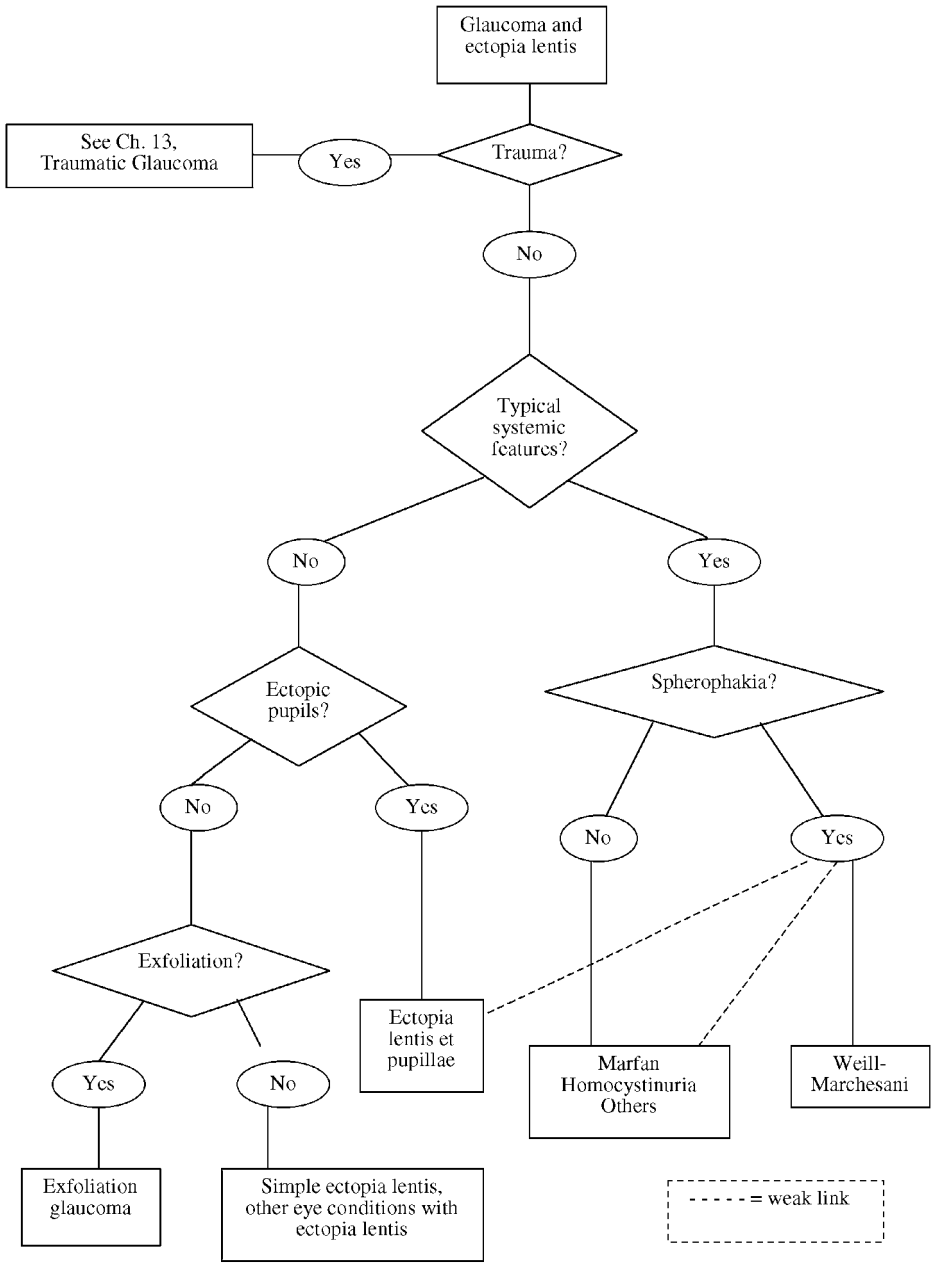

Figure 10–1. Glaucoma and ectopia lentis: differential diagnosis.

Can Ectopia Lentis be Nontraumatic?

For nontraumatic lens dislocations, the diagnostic workup of the glaucoma is similar in most entities.[4,5]

Are There Typical Systemic Abnormalities?

One must elicit a complete medical history to look for specific clinical features that are typical of syndromes associated with ectopia lentis. A referral for a comprehensive medical evaluation is essential. If systemic features are absent, the examination of the pupils will help narrow the differential diagnosis. These features are listed when each entity is addressed separately. One should know the typical clinical components of the most common systemic disorders associated with ectopia lentis as listed in Table 10–1. The importance of this assessment cannot be overemphasized because potentially serious systemic complications can be present when ectopia lentis is first diagnosed by the ophthalmologist. The occurrence and mechanisms of glaucoma in the most common congenital syndromes are compared in Table 10–3.

Are Both Pupils Eccentric ("Ectopic")?

In this case, ectopia lentis et pupillae is the most likely diagnosis. This is an autosomal recessive condition in which both pupils are displaced in one direction and the lenses dislocated in the opposite direction. In some cases the lenses are small and spherical.[5] Peripheral transillumination defects can be present in an iris that dilates poorly. Systemic abnormalities are usually absent. Glaucoma most commonly results from lens dislocation and secondary pupillary block.[4–6] Concurrent ocular pathology includes cataract, severe axial myopia, and retinal detachment. Rarely, these patients may have marfanoid features.[7]

Are the Pupils in Normal Position?

If this is the case, exfoliation syndrome should be first excluded by careful anterior segment biomicroscopy. The presence of a dandruff-like material at the pupillary margin or lens surface and patchy pigment deposition at the angle will alert the examiner. In the absence of exfoliation, the diagnosis of simple ectopia lentis must be entertained. This syndrome is often inherited in an autosomal dominant fashion, although recessive transmission has been documented. The subluxation is usually bilateral, and sometimes asymmetric.[1] The lenses are usually displaced superiorly and laterally and in severe cases they can dislocate into the anterior chamber.[4, 5] The dislocation can occur during the first decade (congenital type) or later in life (spontaneous type). Abnormalities in chromosome 15 (fibrillin gene) have been reported in a congenital case.[8] A paucity of normal zonular fibers has been found in some cases.[9] Glaucoma usually results from lens-induced secondary pupillary block in advanced stages[10] and is more common in the late type of subluxation.[5] Vitreous herniation can play a role in the pathogenesis of the pupillary block. When open, the anterior chamber angle has a normal appearance. Cataracts and retinal detachment can be present.[4,5]

Is Microspherophakia Present?

As the name implies, the lens diameter is decreased and the axial thickness is increased. The most common entity associated with microspherophakia is

Weill-Marchesani syndrome.[4] In addition, a hereditary combination of microspherophakia, ectopia lentis, and glaucoma has been recognized. This triad can also be associated with Marfan syndrome, homocystinuria, and other syndromes not usually linked to microspherophakia.[5] Microspherophakia can also occur as an isolated feature.[11]

Does the Patient Have Systemic Features Typical of Weill-Marchesani Syndrome?

This autosomal recessive syndrome has striking phenotypic features that contrast with those seen in Marfan patients. Patients are short and stocky, with brachycephalia and a depressed nasal bridge. The hands and fingers are short and stubby, and the joints lack good mobility.[5]

What Is the Pathogenesis of the Glaucoma in Weill-Marchesani Syndrome?

Glaucoma occurs more often in Weill-Marchesani syndrome than in Marfan syndrome or homocystinuria,[12,13] usually during the third or fourth decade of life. The dimensions of the lens (25% smaller, 25% thicker)[4] create zonular elongation, rupture, and lens dislocation. Anterior migration of the lens usually induces glaucoma either by blocking the pupil posteriorly or by total luxation into the anterior chamber.[12,14] In recurrent or chronic pupillary block the apposition of the peripheral iris to the cornea can result in peripheral anterior synechiae (PAS) and trabecular damage. In some cases, glaucoma occurs in the absence of lens dislocation, suggesting an open-angle mechanism (trabecular or angular abnormality).[12] In the presence of elongated zonules, mid-dilation can precipitate acute angle-closure glaucoma even in the absence of ectopia lentis.[15] Abnormal anterior chamber angles (abundant iris processes, iris root fraying) have been described but are not specific of this syndrome.[16]

Does the Patient Have Features Typical of Marfan Syndrome?

Patients with this autosomal dominant syndrome are tall, with slender fingers and toes (arachnodactyly), hyperflexible joints, and severe scoliosis resulting in pectus excavatum.[5] Mutations on chromosome 15 can affect the synthesis of fibrillin, a connective tissue protein present in the zonules.[17] Chromosome 5 mutations have also produced a similar syndrome.[18] Cardiovascular abnormalities include aortic dilatation and dissecting aneurysm as well as mitral valve insufficiency.[5]

What is the Pathogenesis of the Glaucoma in Marfan Syndrome?

Marfan syndrome is associated with ectopia lentis in up to 80% of cases.[4] The lens is usually displaced superiorly and frequently temporally. The lens zonules are reduced in number but structurally normal, which explains the

low rate of progression of the dislocation, about 7.5%.[19] As a result, glaucoma is not a common occurrence in Marfan syndrome, its incidence ranging from 5 to 8%.[4,13,20] Pupillary block from lens dislocation has traditionally been thought of as the most common mechanism of glaucoma.[5,13] Several abnormalities of the angle[4,21] have been observed, such as a hypoplastic ciliary muscle, insertion of the longitudinal fibers onto the trabecular meshwork, and an apparent anterior iris insertion. In addition, Schlemm's canal appears discontinuous, showing in some areas more than one channel.[4] Interestingly, one report has suggested that open-angle mechanisms may be more common than previously thought.[20] In addition, 15% of Marfan patients who undergo cataract extraction later develop open-angle glaucoma, a higher incidence than in nonoperated patients.[4]

Does the Patient Have Features Typical of Homocystinuria?

Some systemic features of homocystinuria are similar to those of Marfan syndrome. Patients are tall and slender, with fair skin and hair.[4] Arachnodactyly is less marked than in Marfan syndrome. Mental retardation is present in 50% of cases,[5] and the occurrence of multiple thromboembolic phenomena can be life threatening, especially after general anesthesia.

What Is the Pathogenesis of Glaucoma in Homocystinuria?

Bilateral, symmetrical ectopia lentis is slightly more common in homocystinuria than in Marfan syndrome (90% vs. 80%).[4] Lens displacement occurs earlier in life and is usually inferior and lateral. In contrast to Marfan syndrome, the lens zonules in homocystinuria appear to be structurally abnormal.[5] As the zonules disintegrate, the lens subluxation often progresses to total dislocation.[13] The lens may migrate into the anterior chamber in up to 50% of cases, and posterior migration into the vitreous cavity is not uncommon.[22] As a result, glaucoma is more common in homocystinuria than in Marfan syndrome[4] (23% vs. 8%) and usually results from pupillary block. Angle abnormalities have not been reported[1] (see Table 10–3). Glaucoma can result after cataract extraction, but not as frequently as in Marfan syndrome.

Treatment and Management

How Is Glaucoma Associated with Ectopia Lentis Managed?

The treatment is dictated by the mechanism causing the disease, the most common being pupillary block. Open-angle mechanisms may coexist with pupillary block and are addressed separately. Figure 10–2 outlines the treatment choices based on the clinical picture.

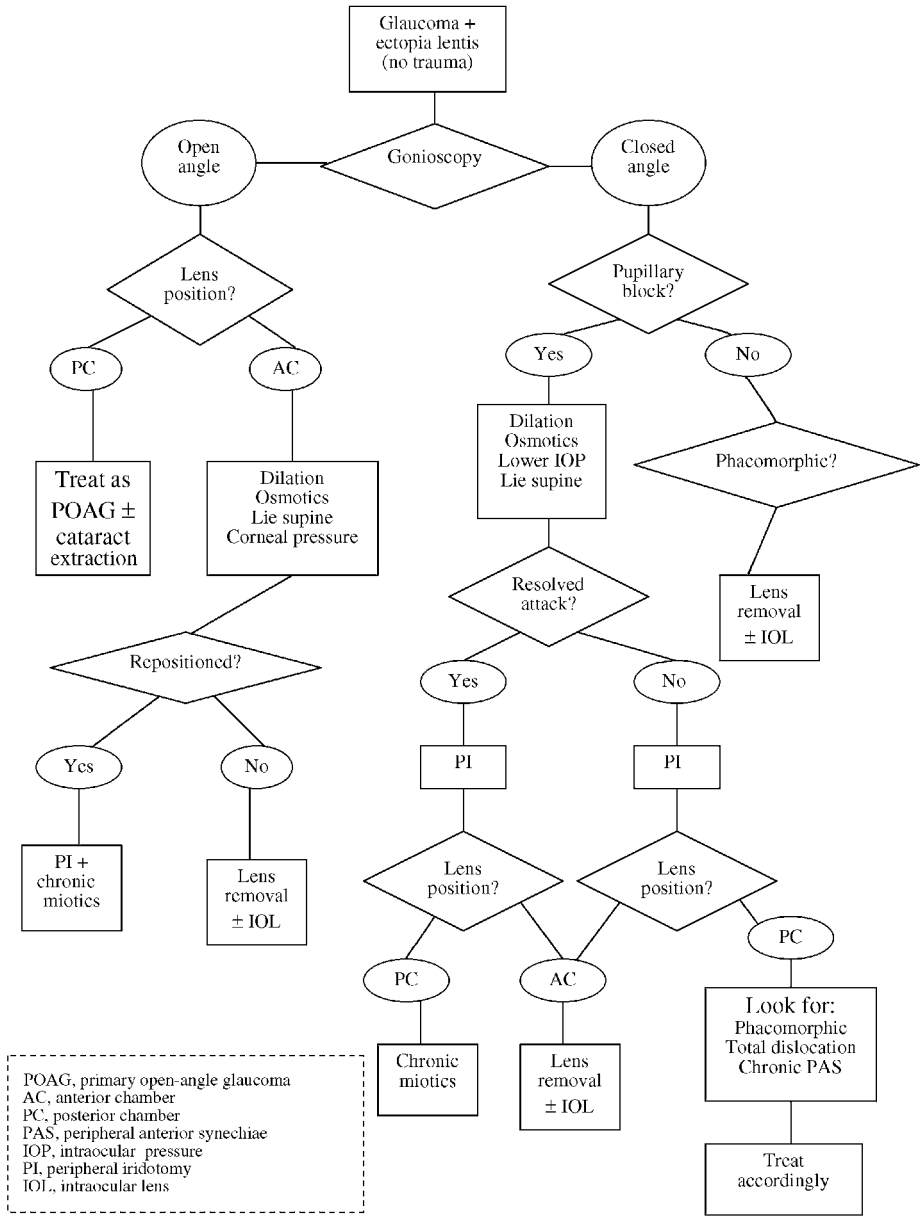

Figure 10–2. Glaucoma and ectopia lentis: management.

Is There Pupillary-Block Angle-Closure Glaucoma?

In this situation the luxated or subluxated lens prevents the free flow of aqueous humor across the pupil into the anterior chamber. Aqueous accumulates behind the iris, pushing its peripheral portion against the trabecular meshwork.[1,4] The speed and extent of the anterior migration of the lens will determine the clinical presentation and the treatment strategy.

The initial treatment of pupillary-block glaucoma in ectopia lentis includes placing the patient in a supine position, promoting vitreous dehydration with osmotic agents, and reducing IOP with beta-blockers, carbonic anhydrase inhibitors, and other drugs. These measures facilitate posterior migration of the lens away from the pupil[1,4] but may have limited success.[22] A peripheral iridotomy is usually performed to treat the pupillary block. The next treatment decision to be made depends on the location of the lens at the time of presentation.

Is the Lens Still in the Posterior Chamber?

In this case the lens should be moved away from the pupil. As a general rule, maximal pupillary dilatation will decrease the area of lens-iris contact, therefore diminishing the degree of pupillary block.[1,4] Cycloplegics are useful to pull the iris-lens–ciliary body diaphragm back. These two actions, in addition to the initial measures, promote posterior displacement of the lens and may relieve the pupillary block. On the other hand, maximal pupillary dilatation may allow the passage of a completely dislocated lens through the pupil into the anterior chamber, an unwanted occurrence.[4]

Regardless of the success of the initial measures, the pupillary block can be overcome by creating a peripheral iridotomy (PI), usually with the neodymium: yttrium-aluminum-garnet (Nd:YAG) laser.[1,4] If gonioscopy reveals no PAS, these patients can be placed on chronic miotic therapy to keep the lens behind the iris.[4] A PI alone may not prevent subsequent anterior dislocation.[22] If in addition the dislocated lens is creating a phacomorphic component (direct anterior pressure on the peripheral iris), lens extraction may be necessary. The PI will not be enough to resolve the angle closure in these cases. After the attack has been broken in the involved eye, prophylactic iridotomy should be performed in the fellow eye.[4,22]

If on the other hand post-PI gonioscopy reveals significant PAS or if trabecular damage is suspected, the management is dictated by the level of IOP and the degree of lens malposition. Visual disability from the dislocation is an additional factor to consider. If the dislocated lens can be kept in the posterior chamber, then medical treatment and filtering surgery can be sequentially used to control the IOP. Again, if the dislocated lens is adding a phacomorphic component and the IOP is uncontrolled, lens extraction becomes necessary.

In cases of microspherophakia (usually Well-Marchesani syndrome), an iridotomy can be placed prophylactically whether or not pupillary block has occurred.[4] In general, miotics are not recommended because they relax the weak zonules, promoting anterior migration of the lens, and increasing the contact between iris and lens, therefore worsening the pupillary block[1,15] ("inverse glaucoma"). Maximal pupillary dilation is the initial recommended strategy since mid-dilation of the pupil has been known to cause bilateral pupillary-block angle-closure glaucoma.[15] Peripheral iridoplasty has also been tried successfully in the treatment of angle-closure glaucoma in Weill-Marchesani syndrome.[23] For description and complications of peripheral iridoplasty, see Chapters 12 and 19.

Is the Lens in the Anterior Chamber?

In this case, if the lens is clear and pupillary block is not present, the initial management can be conservative. An attempt to reposition the lens can be made by maximally dilating the pupil and placing the patient in a supine position. Manual indentation of the central cornea has been successful as an adjunctive measure.[24] If these measures are successful, a laser PI will prevent the recurrence of pupillary block, and chronic miotics will keep the lens in the posterior chamber. If these measures fail (the clear lens remains in the anterior chamber or adheres to the cornea) lens extraction is indicated to prevent further complications.

If pupillary block is present, the condition represents a true emergency because the IOP is usually very high. Delayed treatment will result in irreversible damage to the nerve, cataract formation, or corneal decompensation. The block occurs between the anterior iris and the posterior surface of the dislocated lens or as a direct pupillary occlusion by an entrapped lens. Initial measures should include hyperosmotics, aqueous suppressants, and placing the patient in a supine position. A laser PI can next be performed to relieve the pupillary block.[1,4]

If these measures are successful, the IOP will decrease and the anterior chamber will deepen as the angle opens. One then faces the following therapeutic alternatives. If the lens is cataractous, miotic therapy can keep the lens in the anterior chamber in preparation for lens extraction via a limbal approach. If the lens is clear, maximal pupillary dilatation after the resolution of the pupillary block may allow the lens to fall backward, and then it is managed with miotics as described above. If the lens remains in the anterior chamber despite medical therapy and PI, lens extraction is indicated.

Future Considerations

The key to successful management of this condition is early diagnosis. Prompt referral to an ophthalmologist will prevent life-threatening complications that can occur with some congenital syndromes. New techniques and instrumentation have made the surgical management of these conditions much safer. At this time, pars plana vitrectomy techniques with ultrasonic lens fragmentation offer a successful alternative both in adults[25] and in children.[26]

GLAUCOMA ASSOCIATED WITH CATARACT FORMATION

Definition

How Is Glaucoma Associated with Cataract Formation Defined?

Cataract and glaucoma can be present in an eye in three different situations: (1) they can coexist independently, (2) both can be the result of the same pathologic process (e.g., trauma, inflammation), and (3) one can be the result of the

other one. This section specifically addresses the third situation, where glaucoma is in some way the result of cataract formation or its complications.

Epidemiology and Importance

Both glaucoma and cataract independently increase in prevalence with age; therefore, they commonly coexist in the elderly. The Beaver Dam Eye Study evaluated these two issues in a large population study.[27, 28] The overall prevalence of primary open-angle glaucoma (POAG) was 2.1%, ranging from 0.9% in persons 43 to 54 years of age to 4.7% in persons 75 years of age and older.[27] There was no significant effect of sex after adjusting for age. It is known that the prevalence of POAG is higher in black populations (see Chapter 2). The prevalence of age-related cataracts increased with age for both sexes, with women being more severely affected than men. Overall, 17.3% of patients had nuclear sclerosis and 6% had posterior subcapsular opacities.[28] On the other hand, the occurrence of lens-related glaucoma is strongly linked to the duration of the cataract, with most types of glaucomas occurring in long-standing cataracts.[29-31] Cataracts in the United States are removed relatively earlier than in the developing world. An average preoperative visual acuity of 20/60 was determined in one study.[29] As a result, a lower incidence of lens-related glaucomas can be expected. More specific epidemiologic data is presented when each entity is discussed separately.

We are offered a unique opportunity to successfully treat the glaucoma by addressing the lens condition. With a better understanding of the mechanisms of disease, the terminology has become less confusing. Currently accepted definitions will be used to discuss this fascinating group of diseases.

How Is Glaucoma Associated with Cataract Formation Classified?

Once again, the appearance of the angle and the mechanism of disease represent the major criteria to classify these entities. Table 10–4 outlines the etiologic

Table 10–4. Lens-Related Open-Angle Glaucomas

Type of Glaucoma	Etiologic Factor(s)	Triggering Factor(s)	Offending Factor(s) (In Order of Importance)	Definitive Treatment
Phacolytic	Maturing cataract	↑ Protein solubility Capsule incompetence	Macrophages Lens proteins Inflammatory cells	Lens extraction
Lens particle	Cortex disintegration	Penetrating trauma Surgical trauma	Lens particles Macrophages Inflammatory cells	Lens extraction
Phaco-anaphylactic	Lens matter exposure Immune tolerance	Penetrating trauma Surgical trauma	Inflammatory cells Lens matter Macrophages	Lens extraction
Exfoliative	Unknown	Basement membrane abnormal production	Fibrillar protein and GAGs, etc.	Medical Tx ALT Surgical Tx

ALT, argon laser trabeculoplasty; GAG, glycosaminoglycan.

Table 10–5. Mechanisms of Glaucoma Associated to Cataract Formation

Open-angle glaucoma (lens-induced glaucoma)
Lens particle glaucoma
Phacolytic (lens protein) glaucoma
Phacoanaphylactic glaucoma
Angle-closure glaucoma
Pure pupillary block*
Primary angle-closure glaucoma
Lens enlargement + pupillary block
Phacomorphic glaucoma (intumescent lens)
Angle-closure glaucoma + large cataract (nonintumescent lens)**

*A normal-sized lens in a small globe can generate pupillary block. This in essence represents a type of lens-induced glaucoma.
**A large cataractous lens in a small or normal-sized globe can generate pupillary block, and a mechanical posterior "pushing" (phacomorphic) mechanism can be present as well.

and pathogenic factors involved in the production of the different cataract-related open-angle glaucomas. Table 10–5 describes the various mechanisms of glaucoma associated to cataract formation. Due to the association of phacoanaphylaxis with cataract surgery, this entity is discussed in a different section (see Glaucoma Associated with Aphakia and Pseudophakia, below).

Diagnosis and Differential Diagnosis

How Is Glaucoma Associated with Cataract Formation Diagnosed?

A good history and careful examination are always essential. As we determine the mechanisms of disease acting in a given patient we can then make the appropriate diagnosis and plan the treatment accordingly. Figure 10–3 outlines the diagnostic process and the differential diagnosis of these conditions. The management of these conditions will be discussed separately when each entity is discussed.

Is There a History of Trauma?

Glaucoma associated with ocular trauma is discussed in Chapter 13. Nevertheless two specific clinical entities caused by lens trauma are discussed in this chapter as they represent types of glaucoma essentially caused by lens-related mechanisms. These two are lens particle glaucoma and phacoanaphylactic glaucoma. The status of the lens capsule is the next question to be considered.

Has the Lens Capsule been Violated?

Capsular disruption can result from trauma, either surgical (extracapsular cataract extraction) or nonsurgical (penetrating). In both instances lens particles are released and continuously exposed to the inner ocular environment.[31]

Blunt trauma can in rare instances disrupt the lens capsule, and spontaneous ruptures have also been described. If the capsule has been disrupted, one should suspect the presence of lens material in the anterior segment of the eye. The next step is to determine if there is inflammation and assess the degree and nature of the reaction. If lens particles are seen floating in the anterior chamber, one should suspect lens particle glaucoma (see next section). If significant inflammation with granulomatous reaction is present, the possibility of phacoanaphylaxis must be considered.

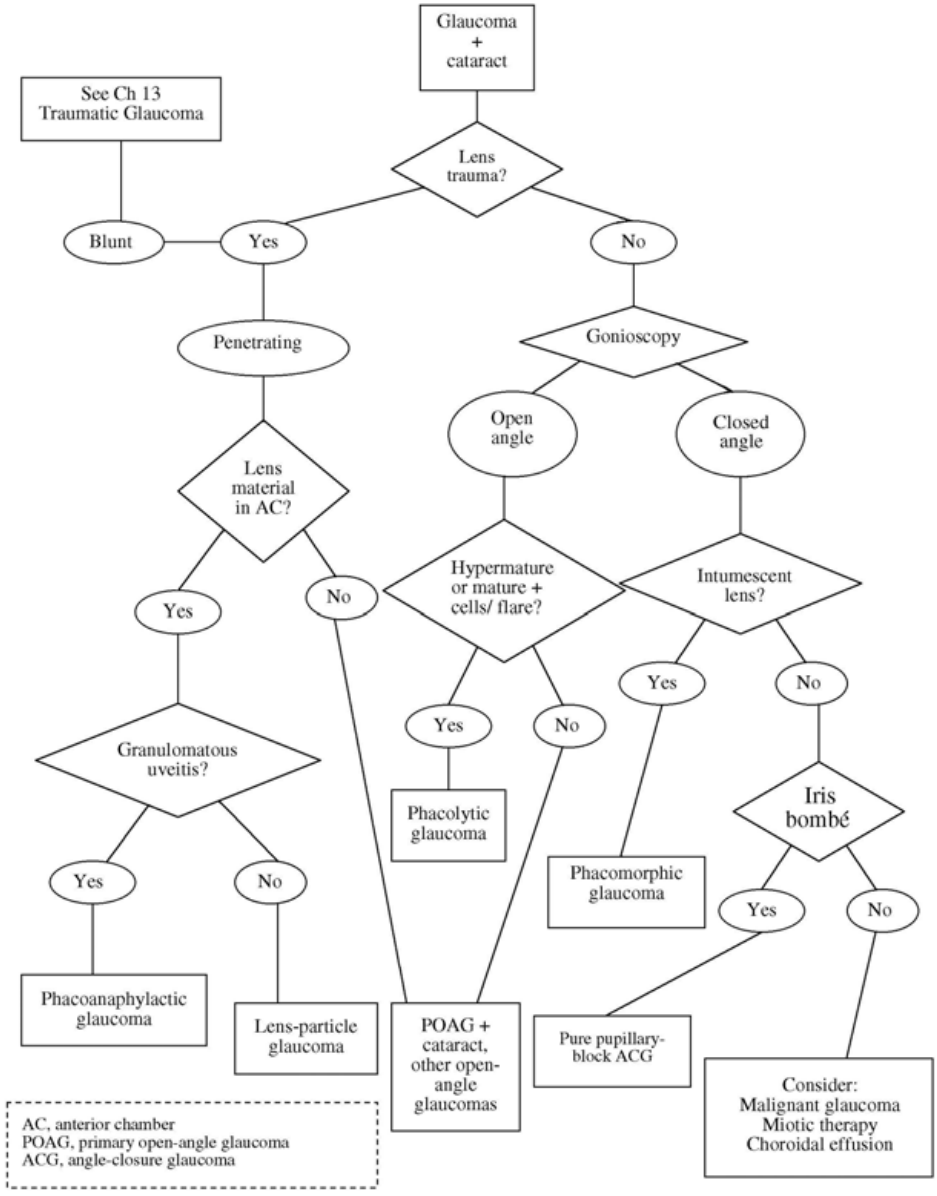

Figure 10–3. Glaucoma and cataract: differential diagnosis.

LENS PARTICLE GLAUCOMA

Definition

How Is Lens Particle Glaucoma Defined?

In this entity the release of lens particles is the result of trauma to the lens. This material circulates in the anterior chamber, blocking the trabeculum and causing a significant IOP elevation.[31]

Epidemiology and Importance

Extracapsular cataract surgery is the method of choice for surgeons in the United States[29] and most countries around the world. Surgeons who operate on the anterior segment know that small amounts of cortex left in the eye cause no significant complications. This material is usually handled by the cellular and drainage mechanisms of the eye.[30] As a result, postoperative IOP elevations and inflammation are usually moderate, transient, and responsive to medical treatment. As surgical techniques continue to improve, lens-related complications will decrease in frequency.

What Is the Pathogenesis of Lens Particle Glaucoma?

In some instances this material adopts a particulate pattern and causes a significant blockage of aqueous outflow.[31] The resulting elevation in IOP is proportional to the amount of material released, stressing the mechanical nature of the obstruction and the resulting glaucoma. Macrophages, inflammatory cells, and debris can add to the blocking effect of the lens matter[30] (see Tables 10–4 and 10–5).

Diagnosis and Differential Diagnosis

How Is Lens Particle Glaucoma Diagnosed?

The glaucoma can occur weeks, months, or even years after the trauma (or surgery).[30] Patients usually present with ocular pain and decreased vision in one eye. White, fluffy lens material can be seen in the anterior chamber in addition to a moderate amount of cells and flare. In extreme cases, a hypopion may be present. The anterior chamber angle is usually open. Macrophages containing lens proteins (as in phacolytic glaucoma) have also been identified[31] and may play a role in further blocking the trabeculum.[30]

In addition to the mechanical obstruction of the open angle by various components, untreated inflammation and its secondary changes (peripheral anterior or posterior synechiae, angle scarring, pupillary membranes, and pigment deposition) can play additional roles in the pathogenesis of the glaucoma.[1,30,31] Cystoid macular edema can result in further visual loss.

What Is the Differential Diagnosis of Lens Particle Glaucoma?

The diagnosis of this condition begins with the documentation of either surgical or nonsurgical lens trauma. Typical fluffy material in the anterior chamber, some inflammation, and elevated IOP with an open angle are strong diagnostic components. The differential diagnosis with other conditions that may mimic lens particle glaucoma are discussed below and illustrated in Figure 10–3.

Phacoanaphylaxis is another entity that can follow traumatic capsular disruption and should be considered in the differential diagnosis. As inflammation is the overriding problem, the IOP tends to be low. In the few cases where the IOP is high, phacoanaphylactic glaucoma results. Granulomatous inflammation with large keratic precipitates strongly suggests phacoanaphylaxis rather than lens particle glaucoma.[30]

In phacolytic glaucoma the lens capsule is grossly intact and a mature or hypermature cataract is present. A history of trauma is not a typical feature of this syndrome. White, fluffy material is not seen because the capsule has not been ruptured. On the other hand, a phacolytic component may be present in lens particle glaucoma if macrophages engulf lens proteins and contribute to outflow blockage.[30, 31] In less typical cases (specially postsurgical), an aqueous sample should be examined to rule out infectious endophthalmitis. An intraocular tumor could seed cells into the anterior chamber, but a thorough preoperative examination should have diagnosed the problem.

Treatment and Management

How Is Lens Particle Glaucoma Treated?

The initial therapy is medical and consists of aqueous suppressants, antiinflammatory drugs, and cycloplegics.[30,31] If prompt improvement does not take place the definitive therapy consists of surgically removing all remaining lens fragments (Fig. 10–4). Delaying intervention can result in entrapment of lens material between capsular flaps or inflammatory membranes, making a late removal more problematic.[30] Acting promptly when patients with a history of trauma or cataract surgery complain of sudden pain or decreased vision will prevent serious complications and permanent visual loss.

Can Nd:YAG Laser Posterior Capsulotomy Cause Lens Particle Glaucoma?

Some patients develop significant IOP elevation and inflammation following Nd:YAG laser posterior capsulotomy.[32,33] Several features place this syndrome apart from classical lens particle glaucoma. First, the small amount of material released by the procedure does not explain an outflow obstruction on a purely mechanical basis. In addition there is no correlation between IOP level and amount of material floating in the anterior segment.[30] It has been shown that the IOP elevation does result from decreased outflow, but the precise mechanism is not fully understood.[33] Small, nonvisible lens particles or vitreous components blocking the trabeculum have been postulated as possible sources of

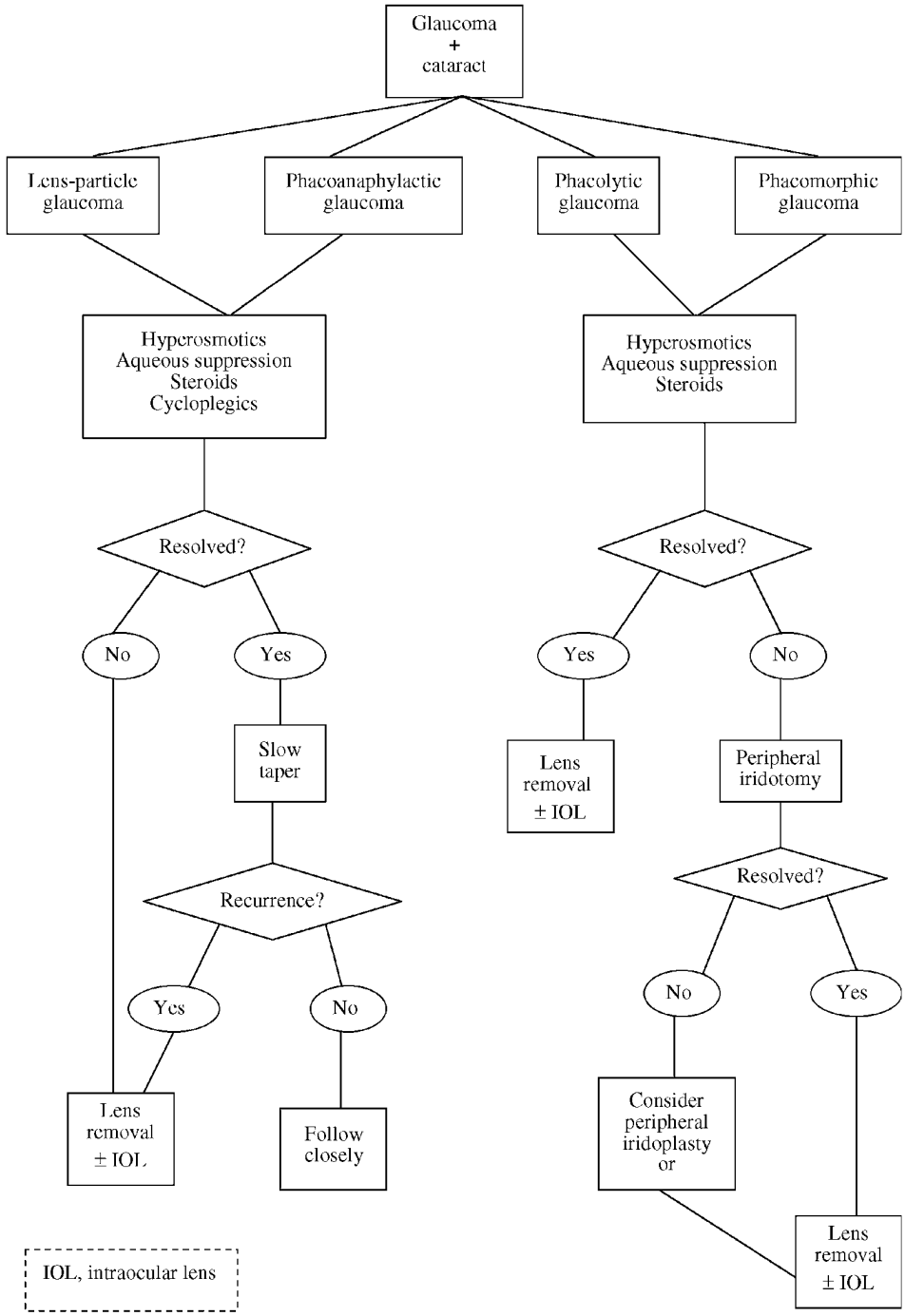

Figure 10–4. Glaucoma and cataract: management.

obstruction.[34,35] It may be better to reserve the term *lens particle glaucoma* for eyes with visible lens particles floating in the anterior chamber. This is not the case in the majority of patients with glaucoma after YAG capsulotomy. A small percentage of these patients will develop full-blown open-angle glaucoma and require conventional long-term medical therapy or filtering surgery.

Future Considerations

With current improvements in surgical techniques, lens particle glaucoma may continue to be seen more often in association with lens trauma than with cataract surgery. In both instances the removal of the lens material may require a more complex approach such as pars plana vitrectomy and lensectomy. It is hoped that future techniques will allow a safer IOL implantation in cases where the entire lens is removed.

Is There a Cataract, But a History of Trauma is Not Present?

When faced with a nontraumatic cataract and glaucoma, a crucial diagnostic element is the evaluation of the anterior chamber angle (see Fig. 10–3).

Is the Angle Open?

If the angle is open, one must carefully examine the lens to determine if one is dealing with a mature or hypermature cataract.

PHACOLYTIC GLAUCOMA

Definition

How Is Phacolytic Glaucoma Defined?

In this condition a particular type of lens proteins (see below) leak through the capsule and along with macrophages block the trabeculum, causing an IOP elevation. Usually a long-standing significant cataract is present.

What Is the Pathogenesis of Phacolytic Glaucoma?

If the cataract is mature or hypermature (rarely immature), the stage is set for phacolytic glaucoma. These cataracts have an increased amount of high molecular weight (HMW) soluble lens proteins.[31] These proteins can leak through microscopic defects in the capsule and circulate in the anterior chamber. Current evidence indicates that the trabecular meshwork is blocked by both HMW proteins and macrophages containing engulfed proteins.[35–37] It has been suggested that these proteins may be more specific and more closely responsible for the outflow blockage seen in phacolytic glaucoma.[31] Crystals of calcium oxalate and cholesterol have also been identified in the anterior chamber[38] (see Tables 10–4 and 10–5).

Epidemiology and Importance

Phacolytic glaucoma is uncommon in the United States, as cataracts are usually removed before they mature.[29] Large series of patients with this entity come from countries where easy access to surgical eye care is not as readily available.[38,39] In one such series, 45 consecutive patients were operated on during a 5-year period with excellent visual results and IOP control.[38] There was no gender preference, and ages ranged from 45 to 85 years. Another series, reporting 44 phacolytic glaucomas and 49 phacomorphic (see next section) glaucomas diagnosed during 1 year, confirms the frequency of lens-induced glaucoma in other parts of the world.[39]

Diagnosis and Differential Diagnosis

How Is Phacolytic Glaucoma Diagnosed?

Because a cataract must be present, this disease usually presents in elderly adults. The sudden onset of open-angle glaucoma in an eye with a mature or hypermature cataract should be considered as phacolytic glaucoma until proven otherwise. These patients present with ocular pain and a prior history of decreased vision due to the cataract. A recent worsening in vision may have occurred.[30] The eye appears injected and the IOP may be markedly elevated, causing corneal edema. The anterior chamber is formed, showing significant flare (soluble proteins) and variable amount of cells. These cells consist of small white cells and larger floating macrophages containing lens proteins.[31] The filtration angle is open and appears grossly normal. The lens is opaque, and in some hypermature cataracts a brunescent nucleus rests inferiorly in a bag of liquefied cortex (morgagnian cataract). The anterior capsule may appear irregular or wrinkled, sometimes with whitish patches on its surface.[31] In some cases the lens may luxate posteriorly, eventually falling into the vitreous cavity.

What Is the Differential Diagnosis of Phacolytic Glaucoma?

Refer to the section on differential diagnosis of lens particle glaucoma, above, for a comparison of phacolytic glaucoma with the most pertinent acute lens-induced glaucoma entities. If the history and examination are consistent and other types of open-angle glaucoma can be ruled out (e.g., neovascular, traumatic, inflammatory), the diagnosis can be reliably made on clinical grounds. If there is doubt, the microscopic examination of an aqueous sample looking for engorged macrophages is indicated. Using the Millipore® filter technique facilitates the identification of the macrophages.[31] False negatives can occur, especially in eyes treated with steroids. Uveitis in the presence of a cataract (but not caused by it) is a major diagnostic category to be ruled out because the extraction of the cataract will cure phacolytic glaucoma but dangerously excacerbate the uveitis. Once again, in these cases the examination of the aqueous humor becomes critical.

As we continue to analyze the differential diagnosis in Figure 10–3 we reach another important question:

Treatment and Management

How Is Phacolytic Glaucoma Managed?

The initial treatment consists of hyperosmotic agents, aqueous suppressants, antiinflammatory drugs, and cycloplegics to temporarily control the disease (see Fig. 10–4). The definitive treatment currently consists of extracapsular extraction of the lens with or without intraocular lens implantation and should be carried out as soon as it is reasonably safe. Unless PAS or trabecular damage is present, the removal of the lens uniformly eliminates the glaucoma and provides excellent visual rehabilitation.[39,40] Although not always feasible, the eye should be open after the IOP has been maximally lowered. If the IOP remains high, a paracentesis should be performed to partially decompress the globe before proceeding.[1] If there is significant zonular dehiscence or difficulty opening the anterior capsule, an intracapsular lens removal[30] with anterior chamber or sutured posterior chamber intraocular lens implantation can be considered. Some surgeons may choose to delay the implantation of the lens until the inflammation has subsided. In one large series the IOL implantation was not a factor affecting the final visual acuity ($p = .18$).[41] Univariate analysis performed in this study showed that patients over 60 years of age with more than 5 days of disease had a higher risk of poor visual outcome. Visual acuity of light perception without projection has not been a poor prognostic indicator in many cases.[39]

Future Considerations

The management of phacolytic glaucoma consists of removing the lens, and the tendency is toward extracapsular surgery with primary IOL insertion.[39,40] The use of viscoelastic materials has allowed a more controlled treatment of the capsule, and small-incision surgery may further improve the visual prognosis in these eyes. Cataract surgery in phacolytic glaucoma will continue to be a challenge.[39]

Is the Angle Closed?

If this is the case, the iris is being pushed against the cornea by either trapped aqueous humor or an enlarged lens. One or both of these components mechanically occlude the angle.

Is the Lens Intumescent?

This can be determined by careful anterior segment biomicroscopy complemented by ultrasonic studies. The axial diameter of the lens is significantly increased. Usually the lens appears white and the cataract is mature. The formation of an intumescent lens can occur over a variable period of time, often becoming noticeable by the pain induced by the elevated IOP. An intumescent lens in the presence of a closed angle is currently known as phacomorphic glaucoma (see Fig. 10–3).

PHACOMORPHIC GLAUCOMA

Definition

How Is Phacomorphic Glaucoma Defined?

This definition implies that the lens is mechanically exerting a direct "pushing" effect on the iris, causing the closure of the angle. This can result from an anteriorly dislocated lens or, most commonly, from an enlarged lens.[1,2]

Epidemiology and Importance

Because phacomorphic glaucoma due to an intumescent lens occurs in cases of advanced, long-standing cataracts, the concepts mentioned in the previous section on phacolytic glaucoma apply to phacomorphic glaucoma as well. Again, this is an uncommon entity in the United States, and large series come from overseas.[41]

What Is the Pathogenesis of Phacomorphic Glaucoma?

In an eye with a nontraumatic cataract and a closed anterior chamber angle, the possibility of phacomorphic glaucoma should be entertained. The term *phacomorphic* has been traditionally associated with an intumescent lens.[1,2,31,35] Intumescence results from influx of water and swelling of the lens cortex, rarely the nucleus. This usually occurs in mature senile, diabetic, uveitic, and traumatic cataracts. The result is distention of the capsule and an increase of the axial diameter of the lens[41] (see Table 10–5).

An enlarged lens can cause angle-closure glaucoma via two mechanisms. First, an increased iris-lens contact results in a relative pupillary block, and second, the enlarged lens can directly push the iris (phacomorphic effect) forward against the cornea, occluding the angle. Usually, whenever phacomorphic glaucoma is present, there is some degree of pupillary block.[42,43] Eyes with narrow angles are more likely to suffer from this type of angle closure.[4,43]

Is the Lens Nonintumescent, But Still Large?

An increase in the axial diameter of the lens can also occur without intumescense, most commonly as a result of a growing cataract. In eyes with narrow angles (hyperopia, small globes with shallow anterior chambers), a phacomorphic component will result from simple lens enlargement, making acute pupillary-block glaucoma more likely.[42] This is probably one of the mechanisms behind primary angle-closure glaucoma. In addition, a clear lens could become "too large" for the eye, acting mechanically to activate the mechanisms previously described. We see how the size of the lens and its spatial relationships with surrounding structures can create circumstances in which a pupillary-block component coexists with a phacomorphic component.[42]

Diagnosis and Management

How Is Phacomorphic Glaucoma Diagnosed?

The diagnosis is usually based on the clinical examination. We should suspect phacomorphic glaucoma in any eye with angle-closure glaucoma and an advanced cataract. Usually the vision is poor, the patient is in pain, and the eye is injected. The cornea can be edematous due to the increased IOP.[4] The angle appears closed and cannot be opened upon reasonable corneal indentation. Low-grade inflammation can sometimes be observed in a uniformly shallow anterior chamber. If the examination of the fellow eye reveals a deeper central anterior chamber, it is likely that lens swelling is present in the involved eye.[4]

On clinical examination what differentiates phacomorphic glaucoma from pure pupillary-block glaucoma is the equal shallowness of the axial and peripheral anterior chamber. In pupillary block the iris bombé gives the axial chamber a greater depth than in phacomorphic glaucoma. An intumescent lens is commonly seen, but a totally dislocated lens in the posterior chamber can be present. Ultrasound biomicroscopy can neatly delineate the various surfaces involved in the pathogenesis of this and other types of angle-closure glaucoma.[44]

What Is the Differential Diagnosis of Phacomorphic Glaucoma?

Figure 10–3 illustrates the thinking pathway as we deal with patients with cataract and angle-closure glaucoma. Other causes of angle closure should be first ruled out. Usually a good history and a detailed anterior segment examination will identify traumatic glaucoma, neovascular glaucoma, exfoliation glaucoma, phacolytic glaucoma, and the various types of angle-closure glaucoma. In addition, the differential diagnosis includes miotic therapy, aqueous misdirection, and uveal effusion, all of which can exert the same effect on the iris and angle.[42] As the view of the posterior pole is impeded by the cataract, a B-scan should be done to rule out a retrolenticular tumor causing the anterior displacement of the lens.[45] Ultrasonography will also identify choroidal effusions and iris cysts, which can result in angle-closure glaucoma.[44]

Treatment and Management

How Is Phacomorphic Glaucoma Managed?

As in other entities discussed in this chapter, it is desirable to reduce inflammation and IOP medically before definitive surgical treatment is undertaken. The initial treatment, therefore, consists of hyperosmotics, aqueous supressants, and antiinflammatory agents. Cycloplegics may not be able to deepen the anterior chamber and may further crowd the angle. Miotics can worsen the pupillary block or create one by pulling the iris-lens diaphragm forward. The definitive therapy consists of removal of the lens with or without IOL placement.[4,31,42] If the IOP can be medically controlled and a large intumescent lens is present, lens removal can be the first and definitive surgical approach.

It appears that in most cases there is a significant component of pupillary block; therefore, a YAG laser PI is indicated as an effective way of lowering the IOP to safe levels.[4,42,46] If the pupillary block is broken and the IOP controlled, lens extraction can be performed under safer circumstances. A reasonable approach, therefore, would consist of medical treatment initially with a PI to follow in preparation for cataract removal. If a PI does not open the angle, then removal of the lens should be performed. Laser peripheral iridoplasty has also been suggested as an option for some phacomorphic glaucomas,[4,47] but is not widely used in this setting.

In the presence of a visually significant cataract, the goals are to visually rehabilitate the eye and prevent permanent optic nerve and trabecular damage as well as peripheral anterior synechiae. Lens extraction under the best possible circumstances will achieve all these goals. The removal of an intumescent lens poses particular challenges as the milky cortex will leak out as soon as the anterior lens capsule is perforated. Initial decompression of the lens and generous use of viscoelastic material usually permits a more controlled anterior capsulotomy. Successful continuous-tear capsulorhexis has been performed using this technique, allowing in-the-bag IOL placement.[48]

Future Considerations

New techniques and viscoelastic use allow safe management of these eyes. When safe extracapsular surgery cannot be performed, pars plana lensectomy with anterior chamber or sutured IOL placement will continue to be an appropriate alternative.

GLAUCOMA ASSOCIATED WITH EXFOLIATION SYNDROME

Definition

How Is Exfoliation Syndrome Defined?

Exfoliation syndrome (ES) is a systemic basement membrane disorder that results in the production and deposition of abnormal material throughout the eye and other system organs. In conjunction with the lens abnormalities, a particular type of secondary open-angle glaucoma results in some patients.[49,50]

Epidemiology and Importance

The reported incidence and prevalence of this disease has significantly increased in recent years across the racial spectrum.[51–56] An increased awareness of the disease and more thorough examinations under full pupillary dilatation partially explains this trend.[57] Despite these data, the prevalence of ES in the general population remains linked to racial and ethnic factors, varying from almost zero among Eskimos to about 25% in Scandinavia and 38% in Navaho Indians.[49,58] The prevalence of ES markedly increases with age in all

races and ethnic groups.[54,55,59] In the United States the Framingham Eye Study found ES in 0.6% of persons between 52 and 64 years of age and in 5% of persons between 75 and 85 years of age.[60] African Americans have a lower prevalence of ES than European Americans of Scandinavian descent.[61] Some reports indicate that ES may be more common in females,[62] but others have shown no difference between the two sexes.[61] No hereditary pattern has been determined in ES.[63] Exfoliation syndrome has been described in a 17-year-old girl with congenital glaucoma who had undergone trabeculectomy and PI in infancy.[64] This report linked iris surgery to the occurrence of ES.

What Is the Prevalence of ES in Patients with Glaucoma?

The reported average prevalence of ES in U.S. glaucoma populations is approximately 12%.[65, 66] Overseas this prevalence has varied from 1.4%[67] to 75%[68] and higher, reflecting the geographic and ethnic variability of this disease. A study from Spain found ES in 243 (44.5%) of 546 eyes with open-angle glaucoma.[69]

What Is the Prevalence of Glaucoma in Patients with ES?

The presence of ES markedly increases the incidence and prevalence of elevated IOP and glaucoma in a given age population.[69–71] The frequency of glaucoma in ES populations varies from 7%[62] to 48.9%.[72] It has been suggested that ES may be a glaucoma risk factor on its own, independent of the IOP elevation documented in these patients.[73] In longitudinal studies eyes with ES and normal IOP have a 5.3% probability of developing glaucoma in 5 years and 15.4% in 10 years. Thus, ES patients have a ten-fold increased risk of having or developing glaucoma compared with the general population.[49] Higher figures have been reported.[74]

Diagnosis and Differential Diagnosis

How Is ES Diagnosed?

To a careful examiner the diagnosis of ES with a fully dilated pupil in an elderly patient should pose no difficulty.[75] Early subtle signs can be detected in the absence of elevated IOP or full-blown features.[76] The disease is in essence bilateral.[77] Bilateral involvement has been more commonly reported in Europe[78,79] than in the United States.[62,80]

The most striking feature is the presence of a dandruff-like white-gray material found more often on the anterior lens surface but actually distributed throughout the anterior segment. A granular sheet of this material can result from accumulation on the lens capsule.[49,50,81] The continuous rubbing by the posterior iris wipes off the midperipheral portion of this material, leaving a central circle and the periphery intact.[49] Rolled-up edges can often be seen at the margins. Exfoliation material commonly sits on the pupillary margin, giving the examiner a first diagnostic clue even before dilatation.[82] ES material may also be seen on the iris, corneal endothelium, anterior chamber angle, lens zonules, and ciliary body. In addition it can be seen on the anterior vitreous

face in aphakes[83] and on intraocular lenses in pseudophakes.[84] Involvement of the lens zonules results in their fragility and disruption.[81,85] Partial or total lens dislocation can occur in advanced cases.[49] Zonular weakness is a predisposing factor for intraoperative complications such as capsular rupture and vitreous loss during cataract surgery.[86] A shallow anterior chamber due to weakened zonules may be present preoperatively.

As a result of the continuous rubbing of the posterior iris epithelium by the granular material, pigment is released into the anterior chamber. This pigment can be seen on the endothelium, anterior iris surface, and filtration angle. At the angle that is usually open, the pigment adopts a patchy configuration in contrast to the solid pattern seen in pigmentary dispersion syndrome.[49,75,76] Pigment deposition can also be seen at Schwalbe's line and in a wavy distribution in front of it (Sampaolesi's line).[50] As pigment is released from the central iris, transillumination defects develop in the area of the iris sphincter,[3,49] but generalized transillumination of the iris has also been described.[87] Ischemia of the iris has been shown by angiographic[88] and fluorophotometric studies.

What Is the Nature of the Exfoliation Material?

Exfoliation material is an irregular meshwork of randomly oriented cross-banded fibrils within a loose fibrogranular matrix.[49,89] It probably consists of macromolecules with protein and polysaccharide components.[90] The precise biochemical nature of the material is not known, but there is evidence of the presence of glycosaminoglycans, fibronectin, chondroitin sulfate proteoglycans, amyloid P protein, and type IV collagen.[49] Current data suggests that the exfoliation material is the result of an abnormal production of basement membrane, taking place in various eye structures and elsewhere in the body. Evidence of the production of this material has been found in the iris, lens, vascular endothelium, perivascular tissues, and zonular apparatus, among others. Extrabulbar and systemic production has also been documented.[49,50,81]

What Is the Pathogenesis of Glaucoma in ES?

Glaucoma occurs primarily through a secondary open-angle mechanism consisting of trabecular blockage by the exfoliation material and pigment.[49,81,91] In addition, damage to the trabeculum[49] and the juxtacanalicular tissue adjacent to the inner and outer walls of Schlemm's canal[92] can result from the deposition of the material. Exfoliation glaucoma can coexist with POAG in many patients. In contrast to most cases of POAG, exfoliation glaucoma can present as an acute open-angle glaucoma with corneal edema and very high IOP, in up to 25% of the cases.[93] These eyes are congested, and if the anterior chamber is shallow they grossly resemble acute angle-closure glaucoma.[91]

Acute angle-closure glaucoma (ACG) in ES is less frequent than open-angle glaucoma.[49] However, reports have documented an increased prevalence of occludable angles and ACG in patients with ES.[94] Secondary angle closure in association with the use of miotics in ES has been reported.[95] In eyes with narrow angles and ES, the acute glaucoma can be precipitated by weak zonules,

allowing an anterior displacement of the lens. A similar mechanism produces the glaucoma associated with microspherophakia. The iris in ES is rigid, and an increased adherence to the pupil caused by the exfoliation material could further promote secondary pupillary block.[96] Finally, ciliary block ACG (malignant glaucoma) has been reported in two patients with ES, presumably as a result of anterior lens displacement.[97]

Acute IOP elevations can occur in patients with ES when vigorous pupillary dilatation is induced. Sudden trabecular blockage by a large amount of released pigment is the explanation for this phenomenon.[98] Marked elastosis of the lamina cribrosa in patients with exfoliation glaucoma has been found,[99] suggesting that an intrinsic abnormality may render these optic nerves more susceptible to glaucomatous damage.

What Is the Differential Diagnosis of ES?

ES must be distinguished from pigmentary dispersion syndrome (PDS). This can usually be done without difficulty after a detailed examination. PDS occurs most commonly in myope young males. A Krukenberg spindle is usually present. Transillumination defects are midperipheral and radial in distribution, not central and patchy as in ES. Trabecular pigment deposition is usually dense and even. In general, the presence of exfoliation material is the hallmark of ES and makes the differential diagnosis easier. Other causes of lens subluxation can be considered and ruled out as mentioned in the pertinent section of this chapter.

What Are the Systemic Implications of ES?

The systemic nature of ES has been demonstrated by the presence of exfoliation material in the conjunctiva, extraocular muscles, retinal, ciliary and vortex vessels, and later in skin, lungs, liver, kidney, heart, and meninges.[100–102] Despite extensive work in this area, no specific clinical entity has been reported to occur in the extraocular system as a result of ES.[49,81]

Treatment and Management

How Is Exfoliation Glaucoma Treated?

The lens is not the only source of exfoliation material; therefore, it is not surprising that the removal of the lens does not cure the glaucoma.[1,4] Exfoliation glaucoma is otherwise treated in a manner similar to POAG. Therefore, the initial approach is medical, stepping up and adding antiglaucoma medications as needed to achieve a "target" IOP. The response of exfoliation glaucoma to medical therapy is less consistent and sustained than in POAG.[103–107] There may be an insufficient "depot" function of topical drugs in the eyes of patients with exfoliation glaucoma. In one study, continuous delivery of pilo-

carpine achieved better IOP control than a four times a day schedule in patients with exfoliation glaucoma, suggesting that less drug is available between doses, resulting in a decreased hypotensive effect.[104] Miotics may have the additional theoretical advantage of reducing the mechanical rubbing of the posterior iris surface, limiting the amount of pigment and exfoliation material released.[49]

When medical therapy fails, argon laser trabeculoplasty (ALT) has been effective in reducing IOP in these patients. The initial response has been in some cases greater than in POAG,[105,108] but the long-term outcome has been similar for both groups.[109] Others have reported a poorer response to ALT in exfoliation glaucoma.[93] There may be an increased risk of IOP spikes due to pigment release.[110] If pupillary block is present, an Nd:YAG laser PI would release less pigment than the argon laser.

The next step in the treatment of uncontrolled exfoliation glaucoma is incisional (filtering) glaucoma surgery. At this time partial-thickness techniques with suture modification are the preferred method of treatment. The surgical indications and techniques are basically the same as in POAG. The surgical outcome appears to be similar or better than in POAG.[105] Postoperative complications may be enhanced by the disruption of the blood–aqueous barrier present in ES.[111] The good results obtained with trabeculectomy suggest that surgery could be performed earlier than in POAG, as the failure rate of medical treatment and risks for optic nerve damage are higher.[91] Trabeculotomy has been proposed as an alternative technique in selected cases,[112] and in one series performed better than in POAG.[113]

What Is the Prognosis of Exfoliation Glaucoma vs. POAG?

In general, the course of exfoliation glaucoma is more severe than POAG as IOPs are higher at the time of diagnosis and throughout the disease. Furthermore, the progression of the optic nerve damage and visual field loss is more rapid than in POAG. More of these patients show poor response to medical therapy and a less sustained response to ALT. These results suggest that patients with exfoliation glaucoma may need earlier surgery than patients with POAG.[114]

Future Considerations

There has been more published work on ES than on all the other lens-related glaucomas combined, which reflects our current lack of knowledge about the precise etiology of this condition. A new technique called trabecular aspiration has been used to literally vacuum the trabeculum, removing pigment and exfoliation material.[115] This technique has been used with and without cataract removal and has shown promising results 18 months after surgery.[116] Ongoing clinical research is trying to determine if large-vessel abnormalities (aortic aneurysms) can be related to the presence of exfoliation material in some cases.[81]

GLAUCOMA ASSOCIATED WITH APHAKIA OR PSEUDOPHAKIA

Definition

How Is Glaucoma Associated with Aphakia or Pseudophakia Defined?

Glaucoma can occur in aphakic and pseudophakic eyes through specific pathogenic mechanisms. The denomination of these entities should include the specific mechanism involved, as aphakia or pseudophakia per se do not cause glaucoma. The terms *aphakic glaucoma* and *pseudophakic glaucoma* therefore should not be used alone.[117] This section discusses eyes in which the absence of the natural lens or presence of an IOL is directly related to the occurrence of the glaucoma.

Epidemiology and Importance

The incidences of glaucoma in aphakia and pseudophakia have decreased and increased, respectively, since IOL insertion has become the norm during cataract surgery.[29] Improvements in instrumentation and surgical techniques have had a great impact on the nature and frequency of IOP-related complications in these patients. These days, chronic glaucoma is not expected to result from uncomplicated cataract surgery, whether or not an IOL is implanted.[118] In the past glaucoma was a common cause (30–40%) of enucleation of eyes after complicated intracapsular and extracapsular cataract surgery.[119] With the improvement in IOL design and instrumentation, chronic glaucoma has become a less frequent event, ranging from 2.1%[120] to 4%[121] of cases. As phacoemulsification with in-the-bag IOL implantation becomes the standard technique, it is expected that the incidence of chronic glaucoma associated with extracapsular techniques will continue to decrease.[122]

What Is the Pathogenesis of Glaucoma in Aphakia and Pseudophakia?

Glaucoma in aphakia and pseudophakia is best understood in terms of time of presentation, clinical features, and pathogenic mechanisms (Fig. 10–5).

Open-angle glaucoma can occur at different times after surgery. Early IOP elevations can result from inflammation or the presence of debris, cortical material, hemorrhage, or residual viscoelastic material in the anterior chamber.[118–123] In some cases the IOP rises immediately after uneventful surgery without identifiable cause.[124] Trabecular edema, distortion of outflow channels by sutures, and inflammation have been proposed as possible contributory factors.[125] On the other hand, IOP elevations can take place a few weeks after surgery. Possible causes include vitreous in the anterior chamber, persistent hyphema or inflammation, lens particle mechanism, proteins and macrophages in phacoanaphylaxis, and steroid effect. In eyes without an intact posterior capsule and vitreous hemorrhage, ghost cells can block the trabeculum and cause persistent glaucoma.[118,123] Late causes of open-angle glaucoma after cataract surgery include ghost cell glaucoma, chronic inflammation, late-occurring hemorrhage, Nd:YAG

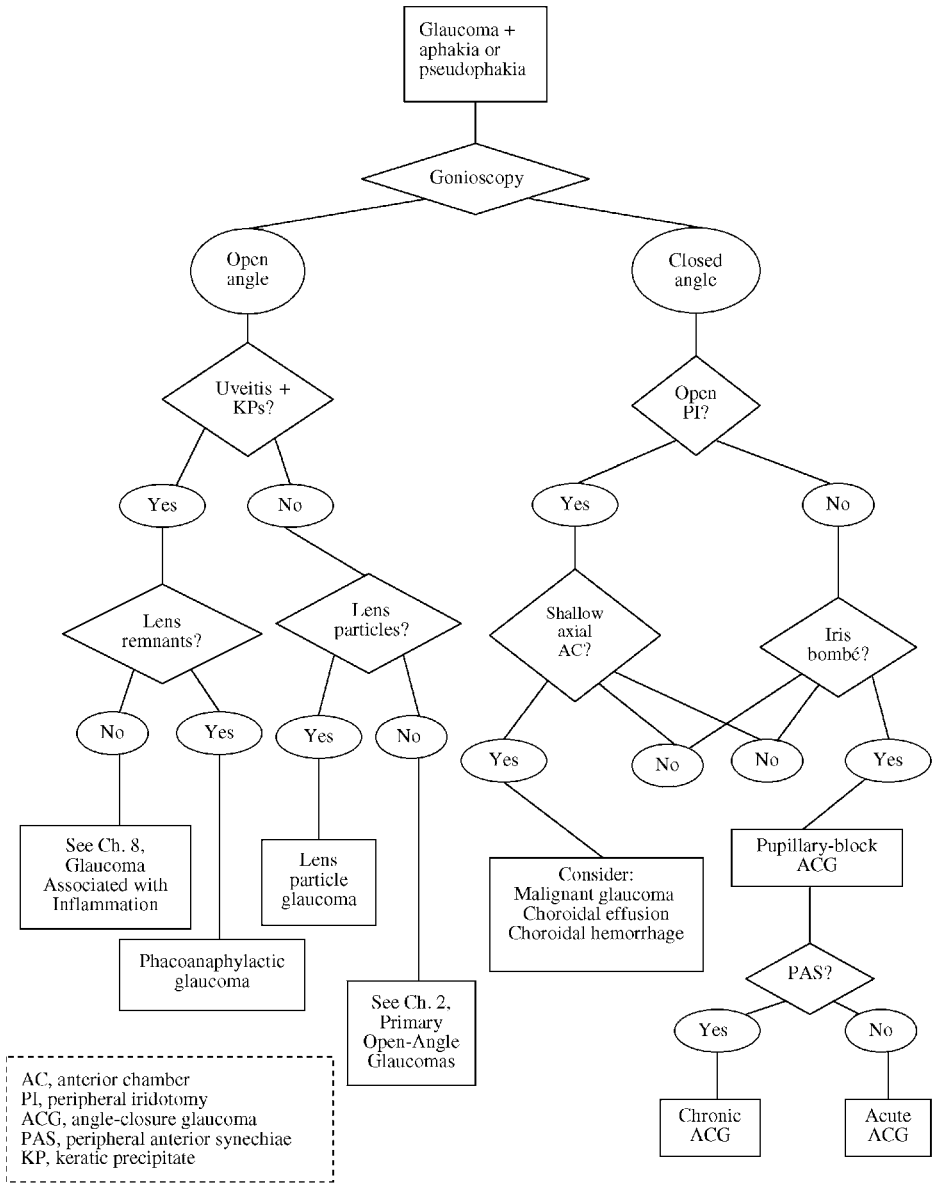

Figure 10–5. Glaucoma in aphakia or pseudophakia: differential diagnosis.

laser capsulotomy,[126] and vitreous in the anterior chamber. Preexistent POAG can cause IOP elevation any time after surgery and should always be suspected when no other cause of the glaucoma is apparent.[125]

Angle-closure glaucoma can result from a number of mechanisms. In the past, flat or shallow anterior chambers and inflammation after intracapsular cataract extraction often resulted in extensive PAS and secondary angle closure. With improved closure techniques and sutures, this complication has become infrequent. Instead, pupillary block is the most common mechanism responsible for ACG in aphakia and pseudophakia.[118,123,127]

Pupillary block in aphakia usually results from vitreous apposition to the pupil when the anterior chamber is shallow and a peripheral iridectomy is absent.[117] In these eyes aqueous misdirection (malignant glaucoma) can be difficult to distinguish from pupillary block. Pupillary block in pseudophakia can be caused by anterior chamber or iris-supported IOLs if a PI was not performed.[128,129] This complication has been reduced, but not eliminated, with current extracapsular techniques and posterior chamber IOL implantation.[130,131] When pupillary block does occur, it can be caused by posterior synechiae to the IOL from inflammation or blood. Capsular components and cortical material can contribute to this process, adhering to the iris or IOL and even blocking an existent PI.[125] In addition, loose vitreous can migrate anteriorly and block the pupil after complicated cataract surgery or after posterior capsulotomy.[132]

In the absence of pupillary block, PAS and ACG may result from prolonged inflammation, hemorrhage, shallow anterior chamber, or faulty wound closure with iris incarceration in the wound.[117, 125] The haptics of anterior chamber IOLs are known to promote PAS formation, although this complication has become less frequent with current lens designs.[125] Fibrous, epithelial or endothelial tissue obliterating the anterior chamber angle can result in postoperative secondary glaucomas (discussed elsewhere in this book).

Diagnosis and Differential Diagnosis

How Is Glaucoma in Aphakia or Pseudophakia Diagnosed?

The diagnostic approach and differential diagnosis outlined in Figure 10–5 refer to subacute or chronic glaucoma. Early, transient postoperative elevations of IOP are discussed previously in this section. Once elevated IOP is confirmed in an aphakic or pseudophakic eye without preexistent glaucoma, the first crucial step is in determining the configuration of the anterior chamber and the angle.

Is the Angle Open?

If this is the case, we should first rule out the possibility of intraocular inflammation as the cause of the glaucoma.

Is Inflammation Present?

If anterior segment inflammation is present, one must determine if residual lens matter is playing a role in the inflammation. In cases of full-blown uveitis and keratic precipitates, a thorough examination after maximal pupillary dilatation may reveal the presence of cortical material. The possibility of phacoanaphylaxis should then be entertained. In the absence of this material, other causes of uveitis should be explored (see Chapter 8).

Treatment and Management

The management of glaucoma associated with aphakia or pseudophakia varies according to the mechanism of disease and the entity in question. Phacoanaphylaxis will be discussed separately, as it involves distinct clinical features and pathogenic mechanisms.

PHACOANAPHYLAXIS

Definition

How Is Phacoanaphylaxis Defined?

Phacoanaphylaxis is an uncommon immunologic and inflammatory condition triggered by the exposure of the internal eye to lens matter. It is essentially a granulomatous uveitis rarely associated with glaucoma.[133] It is discussed in this section because it can occur following cataract surgery.

What Is the Pathogenesis of Glaucoma in Phacoanaphylaxis?

The basic inciting event in phacoanaphylaxis is usually the traumatic disruption (surgical or nonsurgical) of the lens capsule (see Fig. 10–3). The subluxation of an intact lens into the vitreous cavity has been considered another triggering mechanism.[134] It is now thought that somehow the immune tolerance to lens proteins is lost and a granulomatous reaction is initiated by the immune system of the eye, resulting in phacoanaphylaxis.[135]

Open-angle glaucoma can result from trabecular inflammation as well as debris and cells blocking the trabeculum.[28,133] Two basic angle-closure mechanisms take place: peripheral anterior synechiae can permanently occlude the filtration angle, and posterior synechiae can cause secondary pupillary block. In addition, a steroid-induced IOP elevation can take place over the inflammatory glaucoma.[1]

Diagnosis and Differential Diagnosis

How Is Phacoanaphylaxis Diagnosed?

The disease can present hours to months after the lens injury or surgery.[28] The vision is usually reduced and the eye is injected. The severity of the uveitis is variable, but usually keratic precipitates are present and rarely lens material can be seen in the anterior chamber.[1,28] Vitreous inflammation may result from an extension of the anterior uveitis. The offending lens residues can usually be seen. Depending on the duration and severity of the disease, posterior or peripheral anterior synechiae may be already present.[133] In severe, protracted cases, neovascularization of the iris or even phthisis bulbi can occur. If doubt exists as to the nature of the inflammation, an infectious etiology should be promptly ruled out by obtaining aqueous and vitreous samples for examination.

What Is the Differential Diagnosis of Phacoanaphylactic Glaucoma?

The diagnosis of this condition can be difficult, and often is definitively made by histopathologic examination. An aqueous sample may show macrophages similar to those in phacolytic glaucoma.[136] Because trauma to the lens usually precedes both lens-particle and phacoanaphylactic glaucoma, these two conditions can be confused. Fortunately, the removal of all lens material cures both diseases. Inflammation tends to be more significant in phacoanaphylaxis, and large keratic precipitates (KPs) are not usually seen in lens particle glaucoma. A reaction that follows immediately after the injury is most likely to be lens-particle mediated because in most cases a certain time is required for the eye to sensitize to lens components.[28] In bacterial endophthalmitis (posttraumatic or postsurgical) usually a hypopion will be present. Low-grade infectious endophthalmitis caused by *Propionibacterium acnes* or fungi should be considered in delayed cases. Other possible causes include reactions to components used during surgery and phacolytic glaucoma. The presence of inflammation in the fellow eye should raise the suspicion of sympathetic ophthalmia, although certainly more than one mechanism may be acting in the same patient.[133]

Treatment and Management

How Is Phacoanaphylactic Glaucoma Managed?

The initial treatment consists of topical antiinflammatory therapy along with antiglaucoma medications. Almost uniformly the uveitis recurs despite continuing therapy.[28,133] The definitive treatment is the removal of all lens residues from inside the eye. This is currently done via a pars plana approach to gain access to lens material located posteriorly. Often the capsule and therefore the IOL may have to be removed.[28] An anterior chamber or sulcus-placed IOL may have to be removed. Intensive postoperative steroid therapy must be monitored for the possibility of steroid-induced glaucoma. Histopathologic examination of the surgical specimen must then be performed to confirm the clinical diagnosis. If the glaucoma persists after the removal of the lens material, other open-angle or angle-closure components should be appropriately addressed. Glaucoma filtering surgery with antimetabolites may be needed in most of these patients.

After completing our discussion of phacoanaphylaxis we continue to analyze Figure 10–5. We now continue the discussion of glaucoma and aphakia/pseudophakia, and again turn to the question of inflammation.

Is Inflammation Absent from the Eye?

In this case we can diagnose these patients as having POAG in the presence of aphakia or pseudophakia. This category includes cases of preexistent POAG, new-onset POAG, and trabecular damage from previous inflammation, pigment deposition, or other unknown factors. For management purposes, this last group can be grouped to POAG, with some special considerations on a case-by-case basis.

Is the Angle Closed?

If this is the case, the next critical issue is whether or not a functioning PI (or iridectomy) is present. Pupillary block is the most common cause of ACG.

In the absence of an open PI, pupillary block is the most likely acting mechanism. Further certainty exists if a characteristic iris bombé configuration is present (anterior chamber is deeper axially than peripherally). The chronicity of the condition will be reflected by the presence of posterior or peripheral anterior synechiae. Depending on the case, posterior synechiae can form between the iris and the vitreous face, anterior chamber IOL, posterior chamber IOL, or intact posterior capsule. In aphakic eyes the iris bombé configuration is less evident. If this configuration is not present, one should consider the possibility of aqueous misdirection or malignant glaucoma.[127]

If a functioning PI is present, pupillary block is most likely not the mechanism responsible for the angle closure. It is crucial to clearly determine the patency of the PI by paying attention to the opening itself rather than the transillumination defect. If doubt remains, another PI should be performed. The most common entity to cause angle closure in the presence of a patent PI is the so-called malignant glaucoma. The pathogenic mechanism is multifactorial, including posterior aqueous misdirection and ciliary block by vitreous at the ciliary body. Characteristically, the anterior chamber is uniformly shallow and in extreme cases the vitreous or IOL can touch the endothelial surface. This entity is discussed in Chapter 12.

How Is Open-Angle Glaucoma in Aphakia and Pseudophakia Managed?

If open-angle glaucoma is present in aphakia or pseudophakia and it is not related to inflammatory lens-related mechanisms, the management is similar to that of POAG, with some exceptions. First, epinephrine derivatives are usually avoided due to the possibility of inducing cystoid macular edema.[127,137] Second, strong miotics (e.g., cholinesterase inhibitors) can be used more freely as the risks of cataract formation or angle narrowing are less critical. Argon laser trabeculoplasty is the next therapeutic step and can be more effective in pseudophakia than in aphakia but overall less effective than in phakic eyes.[28,138,139]

When glaucoma filtering surgery becomes necessary in noninflamed aphakic and pseudophakic eyes with open angles, several considerations are worth mentioning. First, partial-thickness (guarded) operations with suture manipulation are currently preferred over full-thickness procedures due to the higher rate of complications with the latter technique. Second, due to altered conjunctival and Tenon's capsule anatomy, the procedure is technically more difficult. Areas with mobile, nonadhered conjunctiva should be selected. Third, the rate of intra- and postoperative complications is increased in this group of patients. Finally, the long-term success rate is significantly decreased when compared to phakic eyes, although the precise causes of this phenomenon are poorly understood.[139,140] Drainage devices are an alternative when filtering surgery has failed to control the glaucoma. Cyclodestructive procedures are usually the last resort. The reader is referred to Chapter 19 for a complete discussion of these matters.

How Is Angle-Closure Glaucoma in Aphakia and Pseudophakia Managed?

Only aspects specifically pertinent to the absence of the natural lens or the presence or an IOL are addressed in this section. The reader is referred to specific chapters when a more general approach is indicated.

The initial management of ACG regardless of the mechanisms involved depends on the level of IOP and status of the eye. In acute symptomatic cases, hyperosmotics and aqueous suppressants are indicated. Once the IOP has been lowered and the eye is quiet, any subsequent treatments have a greater chance of succeeding.

If an open PI is not present and an iris bombé configuration strongly suggests pupillary block, the treatment of choice is an Nd:YAG laser peripheral iridotomy. More than one may be needed if posterior synechiae have created loculated pockets of fluid behind the iris. Once the pupillary block has been, overcome the next issue is whether or not PAS is present. If the treatment is prompt, PAS may be prevented. Glaucoma filtering surgery may be necessary if the synechiae persist and less invasive procedures such as peripheral iridoplasty have not been effective. See Chapter 5 for a complete discussion on the treatment of acute and chronic secondary angle-closure glaucoma.

If a typical iris-bombé configuration is not present, or if doing the PI does not change the configuration of the anterior chamber, the possibility of aqueous misdirection should be raised. Of course, if an open PI was present on presentation, this would be the first diagnostic suspicion in a patient with a shallow anterior chamber and elevated IOP. See Chapters 12 and 19 for a complete discussion on malignant glaucoma.

Future Considerations

As practice patterns continue to evolve[29] glaucoma in aphakia will become a rarity. The management of this entity will vary as new drugs and surgical techniques appear. Glaucoma in pseudophakia, on the other hand, may continue to be a challenge. Prevention through improved surgical techniques and early detection are essential to ensure a good visual outcome.

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◆ 11 ◆

Glaucoma Associated with Vitreoretinal Disorders

John J. Alappatt and Albert O. Edwards

There is an intimate association between several vitreoretinal diseases and glaucoma (Table 11–1). Both primary and secondary forms of glaucoma may be encountered. The glaucomatous process may start out as an episode of elevated intraocular pressure (IOP), which may subside after a short course or may persist indefinitely. This discussion follows the outline shown in Table 11–1 and the diagnostic considerations are shown in Figure 11–1.

Table 11–1. Vitreoretinal Diseases and Glaucoma

Retinal vascular diseases
Retinal venous occlusion
Retinal arterial occlusion
Carotid occlusive disease
Diabetes mellitus
Retinopathy of prematurity (ROP)
Coats' disease
Retinal degeneration and dystrophy
Familial exudative vitreoretinopathy
Vitreoretinal syndromes (Stickler's syndrome)
Retinitis pigmentosa (RP)
Age-related macular degeneration (ARMD)
Others
Rhegmatogenous retinal detachment (Schwartz syndrome)
Ciliochoroidal effusion
Vitreous hemorrhage
Myopia

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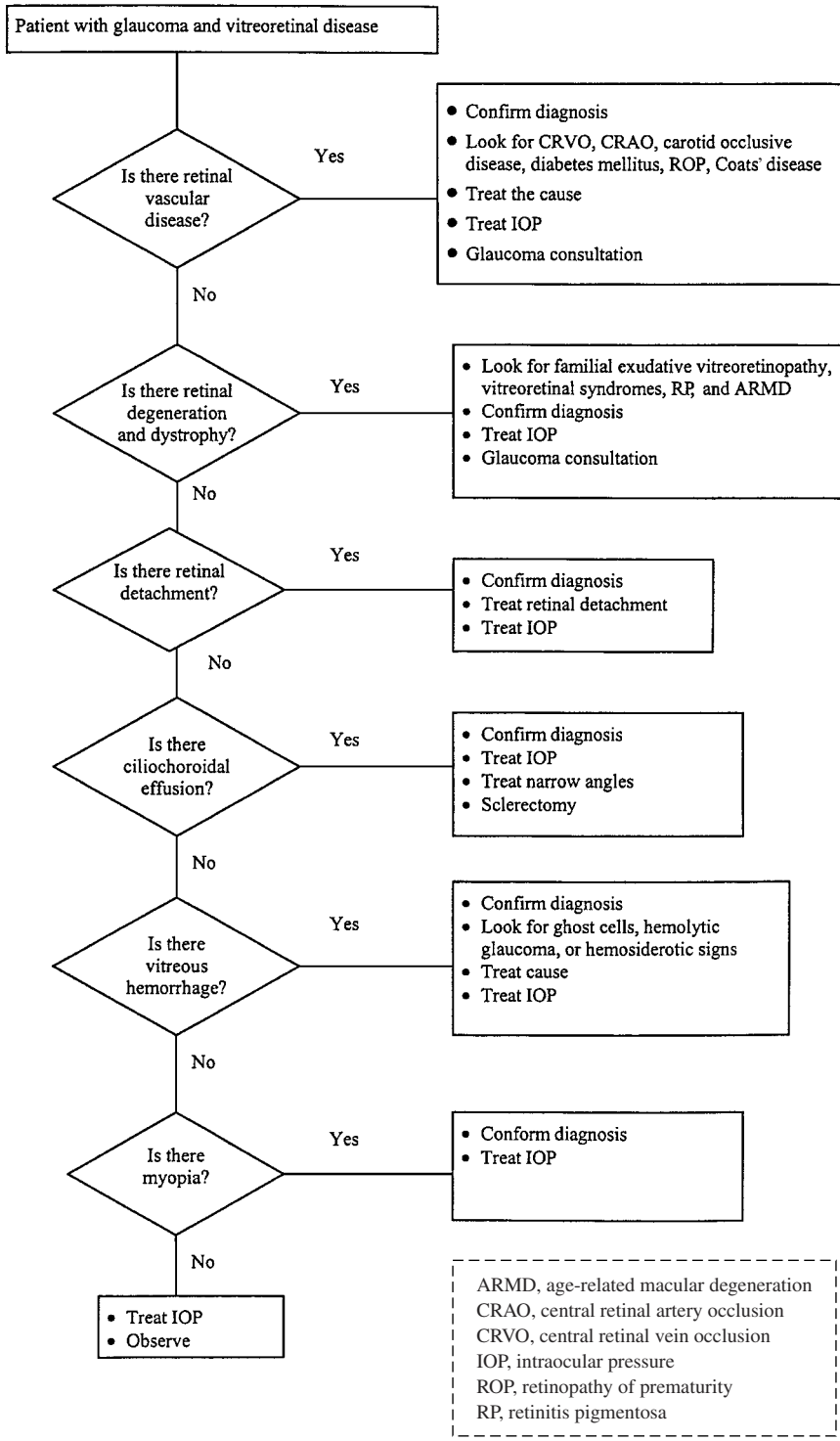

Figure 11–1. Management of a patient with glaucoma and vitreoretinal disease.

RETINAL VASCULAR DISEASES

Definition

What Retinal Vascular Diseases Are Commonly Associated with Glaucoma?

Excluding postoperative glaucoma, retinal vascular diseases represent the most common causes of secondary glaucoma. Ischemic retinovascular diseases give rise to glaucoma through different mechanisms leading to angle closure from neovascularization of the anterior segment, ciliary body rotation, and contracture of retrolenticular tissue. These diseases include each of the six retinal vascular diseases listed in Table 11–1. In addition, open-angle glaucoma can arise in the absence of angle neovascularization in patients with retinopathy of prematurity, diabetes mellitus, and retinal venous occlusions (Table 11–2).

Epidemiology and Importance

How Common Is Glaucoma in Association with the Retinal Vein Occlusion?

Several studies have clearly demonstrated that the incidence of primary open-angle glaucoma (POAG) in patients with central retinal vein occlusion (CRVO) is much higher than in the normal population.[1] Between 10 and 50% of patients with CRVO have been found to have an open-angle glaucoma.[2,3]

The frequency of secondary nonrubeotic angle-closure glaucoma after CRVO is unknown, although a few cases have been reported. Possibly this condition is rarely diagnosed rather than rare.[4]

Table 11–2. Retinal Vascular Diseases

Retinal venous occlusions
Branch retinal vein occlusion (BRVO)
Hemiretinal vein occlusion (HRVO)
Central retinal vein occlusion (CRVO)
Retinal arterial occlusions
Central retinal artery occlusion (CRAO)
Ophthalmic artery occlusion
Carotid occlusive disease
Proliferative diabetic retinopathy (PDR)
Retinopathy of prematurity (ROP)
Coats' disease
Other retinal and choroidal vascular diseases
Choroidal hemorrhage
Choroidal hemangioma
Sturge-Weber syndrome
Sickle cell retinopathy
Syphilitic retinal vasculitis
Radiation retinopathy

The reported rate of neovascular glaucoma in CRVO ranges from 4% to approximately 50%.[5] The Central Vein Occlusion Study Group found that anterior segment neovascularization developed in 16% of 714 eyes.[6] The strongest predictors of development of iris or angle neovascularization were initial visual acuity and amount of nonperfusion seen on fluorescein angiography. If the initial visual acuity is worse than 20/200, prognosis for vision is poor (80% remain at that level or worse); the primary concern is the prevention of neovascular glaucoma by careful attention to the development of iris or angle neovascularization and prompt treatment if it occurs. Because more than one-third of initially perfused eyes with poor vision develop nonperfusion and iris/angle neovascularization, visual acuity is more important than the initial fluorescein angiogram in determining the prognosis and clinical management of the patient.[6]

How Common Is Glaucoma in Association with Central Retinal Artery Occlusion?

Development of neovascular glaucoma has been reported in approximately 15% of patients with central retinal artery occlusion (CRAO). In a prospective study of 33 consecutive patients, 18.2% developed neovascularization of the iris and 15.2% went on to develop neovascular glaucoma.[7]

How Common Is Glaucoma Associated with Carotid Occlusive Disease?

Carotid occlusive disease is a condition in which there is low blood flow through the ophthalmic artery due to blockage in the carotid artery. This condition accounted for 13% of all cases of neovascular glaucoma in one series.[8]

How Common Is Glaucoma in Association with Diabetes Mellitus?

Several large epidemiologic studies have noted an association between diabetes and open-angle glaucoma.[9] The reported prevalence of rubeosis iridis in diabetic patients ranges from 0.25 to 20%.[10] In diabetic patients with rubeosis iridis, the reported incidence of neovascular glaucoma ranges from 13 to 22%.[10–12]

How Common Is Glaucoma in Association with Retinopathy of Prematurity?

Glaucoma associated with retinopathy of prematurity (ROP) often occurs at approximately 3 to 6 months of age. However, angle-closure glaucoma may occur later in childhood, so continued observation is necessary.[13,14] It is estimated that this complication may occur in as many as 30% of eyes with advanced retinopathy of prematurity.[15]

How Common Is Glaucoma In Association with Coats' Disease?

In one series, glaucoma was present in 36 out of 62 eyes (58%) with Coats' disease.[16]

Diagnosis and Differential Diagnosis

How Is Glaucoma Diagnosed in Patients with CRVO?

When a patient presents with acute loss of vision, shallow anterior chamber, elevated IOP, and a hemorrhagic retinal fundus picture, the diagnosis of CRVO complicated with angle-closure glaucoma should be suspected. Unilateral shallowing of the anterior chamber may be secondary to anterior lens dislocation, uveal effusion, choroidal tumors, choroidal hemorrhage, and choroidal and ciliary body detachment, and can follow panretinal photocoagulation.[4] Careful examination with indirect ophthalmoscopy is helpful to make the correct diagnosis. Ultrasonography may be necessary if there is media opacity.

Neovascular glaucoma associated with a CRVO usually occurs within 3 months and has been called "90-day glaucoma." A patient often presents with poor vision, a severely elevated IOP, an open angle with neovascularization of the iris and angle, and a hemorrhagic retinal fundus picture. It is important to perform gonioscopy in order to detect neovascularization of the angle.

How Is Glaucoma Diagnosed in Patients with CRAO?

A patient who suffers an acute central retinal or ophthalmic artery occlusion presents with sudden visual loss, an edematous white retina except in the foveal region, giving a "cherry red spot" appearance, and sluggish flow through the retinal arterioles. After a few weeks the fundus may appear normal; however, the vision remains poor. These patients may develop neovascular glaucoma.

How Is Glaucoma Diagnosed in Patients with Carotid Occlusive Disease?

Patients with carotid occlusive disease will initially present with a low IOP, chronic aqueous flare, and midperipheral dot-blot retinal hemorrhages. Some patients may progress to neovascular glaucoma from iris neovascularization due to ocular ischemia.

How Is Glaucoma Diagnosed in Patients with ROP?

The diagnosis of glaucoma in a small infant with ROP is difficult.[17] When a young child with a history of prematurity presents with a shallow anterior chamber and elevated IOP, the diagnosis of glaucoma associated with ROP should be entertained. Contracture of the retrolental mass in ROP can cause forward displacement of the lens-iris diaphragm with progressive shallowing of the anterior chamber and eventual angle-closure glaucoma.[14] Developmental abnormalities in the anterior chamber may contribute to glaucoma in these patients. In addition, chronic retinal detachment may lead to retinal ischemia and neovascular glaucoma.

How Is Glaucoma Diagnosed in Patients with Coats' Disease?

Coats[18] described a childhood exudative retinopathy in which the primary feature was hemorrhage and exudation from the retinal blood vessels in the sub-

retinal space. Coats' disease was later described as a unilateral, exudative retinopathy resulting from telangiectasia of retinal vessels.[19] This disease usually affects young boys before the age of 8 and occurs unilaterally.[16] Glaucoma associated with Coats' disease was secondary to angle closure, with IOP's ranging from 21 to 60 mm Hg.[16] In one study, 11% of patients with Coats' disease presented with painful glaucoma of sudden onset due to angle closure.[16] The mechanism of angle closure in these patients appears to be due to forward displacement of the lens-iris diaphragm. Neovascular glaucoma may also develop and result in a blind, painful eye.[20]

Treatment and Management

How Is Glaucoma Associated with CRVO Treated?

When CRVO is associated with transient angle-closure glaucoma, the treatment should be medical because the angle returns to normal depth over a few weeks. Unlike primary angle-closure glaucoma, for which iridectomy is the definitive therapy, the treatment of choice for secondary angle-closure glaucoma is medical.[4] Treatment with cycloplegics and aqueous suppressants is recommended. Miotics such as pilocarpine cause a forward shift of the iris lens diaphragm and may worsen the angle closure.

The Central Vein Study Group recommended that patients be followed monthly or bimonthly depending on their visual acuity for the first 6 months to examine the iris and angle for any development of neovascularization.[6] It is important to be aware that angle neovascularization can occur without pupillary margin involvement in CRVO, implying the necessity of screening gonioscopy.[21] Panretinal photocoagulation (PRP) was recommended promptly at the first sign of definite neovascularization, but not prophylactically.[6] Prophylactic PRP did not totally prevent anterior segment neovascularization. Prompt regression of anterior segment neovascularization in response to PRP was more likely to occur in eyes that have not been treated previously.[22] Because of the widespread areas of nonperfusion, posterior segment neovascularization rarely occurs with ischemic CRVO. In 10 of 117 eyes in patients with iris/angle neovascularization, the new vessels failed to regress in response to photocoagulation, and neovascular glaucoma developed in the eye that could not be controlled medically.[6] The treatment of neovascular glaucoma is discussed in Chapter 14.

How Is Glaucoma in Relation to Retinal Arterial Occlusion Managed?

Although PRP has been proposed as a treatment for prevention of neovascular glaucoma in patients with CRAO, in one study, five of six patients with neovascularization of the iris went on to develop neovascular glaucoma despite PRP.[7] However, ablation of the ischemic retina, which may be the source of angiogenic factors, must be undertaken. If the fundus view is adequate, then

thorough PRP should be undertaken promptly. Cryotherapy or transscleral diode laser is useful if the view is poor.

How Is Glaucoma in Relation to Carotid Occlusive Disease Managed?

Carotid occlusive disease may ultimately result in neovascular glaucoma. The role of carotid endarterectomy in preventing neovascular glaucoma is unclear. There are cases of resolution of ocular ischemic findings, but others could not document improvement or stabilization of vision.[23]

How Is Glaucoma in Association with Diabetes Managed?

Management of open-angle glaucoma in association with diabetes is similar to its management in nondiabetic patients. In is prudent to avoid epinephrine and prostaglandin agents in patients with diabetic macular edema.[24–28] One should avoid using oral glycerin to acutely reduce IOP in diabetic patients. Oral isosorbide does not raise blood sugar and is preferable. Advanced diabetic retinopathy with widespread retinal ischemia may result in neovascular glaucoma. The ischemic retina, which is presumed to be producing angiogenic factors, must be treated for anterior segment neovascularization to regress. PRP is the easiest and least invasive method; however, this method is not possible if the view to the posterior segment is obscured by cataract or vitreous hemorrhage. Retinal cryotherapy, which does not require a posterior pole view, may be performed as an office procedure. Any retinal detachment that is present must be surgically repaired followed by laser photocoagulation.

How Is Glaucoma in Relation to ROP Managed?

Management of glaucoma in cases of ROP is difficult.[17] Lens extraction, alone or combined with vitrectomy, has proven helpful in patients with angle closure.[13,29] Cycloplegics may initially be helpful in some cases of angle closure related to pupillary block; however, most cases require lensectomy and vitrectomy for definitive cure.[30] When a chronic retinal detachment is present, neovascular glaucoma often complicates ROP.[31] Treatment may include seton devices and cyclophotocoagulation; however, enucleation may be necessary if the eye becomes blind and uncomfortable.

How Is Glaucoma Associated with Coats' Disease Managed?

Multiple sessions of photocoagulation or cryotherapy of the peripheral retinal telangiectasias is the preferred treatment of eyes with Coats' disease.[32] Angle-closure glaucoma associated with Coats' disease is extremely difficult to treat. Success has been reported using vitreoretinal techniques in order to reattach the retina, destroy the extensive retinal telangiectasias, and drain the subretinal exudates.[20,33,34]

Future Considerations

What Future Therapies May Be Available to Treat Glaucoma Associated with the Retinal Vascular Disorders?

Antiangiogenic drug delivery may be used during or independently of surgery to reduce neovascularization. Endocyclophotocoagulation has become a useful adjunct in treatment of chronic glaucoma.

RETINAL DEGENERATION AND DYSTROPHY

Definition

How Is Glaucoma Associated with Retinal Degenerations and Dystrophies Defined?

Familial exudative vitreoretinopathy, vitreoretinal syndromes such as Stickler's syndrome, retinitis pigmentosa (RP), and age-related macular degeneration (ARMD) are associated with glaucoma (Table 11–1).

Epidemiology and Importance

How Common Is Glaucoma Associated with Retinal Degenerations and Dystrophies?

The incidence of angle-closure glaucoma with ARMD (secondary to massive substantial hemmorhage) is rare. The prevalence of POAG in patients with RP has been reported to range from 2 to 12%,[35] whereas angle-closure glaucoma has been reported to be 1.03% in patients with RP over age 40.[36] In one study of 39 patients with Stickler's syndrome, 10% had ocular hypertension.[37]

Diagnosis and Differential Diagnosis

How Is Glaucoma in Association with Age-Related Macular Degeneration Diagnosed?

Age-related macular degeneration (ARMD) is a common disorder characterized by decreased visual acuity with drusen in the macula occurring in elderly patients. Late forms of this disorder affect approximately 7% of individuals over the age of 75.[38] Patients with exudation may experience massive vitreous, subretinal, or suprachoroidal hemorrhage. Rapid expansion of the subretinal or suprachoroidal space leads to an increase in the posterior segment volume and anterior displacement and rotation of the lens-iris diaphragm, which may result in angle-closure glaucoma. This diagnosis should be suspected in the elderly patient presenting with angle-closure glaucoma and forward displacement of the lens-iris diaphragm without the anticipated shallow chamber in the fellow eye. Ghost cell glaucoma has also been reported following vitreous hemorrhage from ARMD.[39]

How Is Glaucoma in Relation to Retinitis Pigmentosa Diagnosed?

Retinitis pigmentosa (RP) is an inherited retinal degeneration characterized by nyctalopia, attenuated retinal arterioles, and presence of pigmentary changes in the retinal periphery. The diagnosis of glaucoma in the presence of RP can be challenging because both diseases may give a similar field defect. Because most forms of RP are rod-cone degenerations, a generalized constriction of the visual field is seen, which makes detecting glaucomatous scotomas difficult. In addition, the waxy pallor observed in RP can make evaluation of the optic nerve head difficult.

How Is Glaucoma in Relation to Stickler's Syndrome Diagnosed?

Stickler's syndrome, or hereditary arthro-ophthalmopathy, is characterized by arthritis, cleft palate, midfacial hypoplasia, and ocular defects including radial perivascular lattice degeneration, vitreous degeneration, glaucoma, cataracts, and frequent retinal detachments.[40] Phelps[41] noted that several of his patients with Stickler's syndrome had mild to moderate elevation of IOP. The anterior chambers were open without obvious structural malformation. The diagnosis of glaucoma is difficult because lens opacities and high myopia impair the view of the optic disc. In addition, the discs are often tilted, and cupping invariably is shallow. Areas of retinal degeneration may cause visual defects similar to those of glaucoma, and IOP may be the only reliable criterion on which to base treatment.[41]

Treatment and Management

How Is Glaucoma Associated with ARMD Treated?

Angle-closure glaucoma secondary to exudative complications of ARMD may be treated medically with cycloplegia and aqueous suppressants. Cycloplegia may reverse angle-closure glaucoma in this and other posterior segment causes of angle closure, whereas miotics may exacerbate the condition.

How Is Glaucoma Associated with RP Treated?

There is a tendency to treat patients with RP earlier with aqueous suppressants than might otherwise be done in the absence of a definitive diagnosis of glaucoma because of the difficulty in interpreting the visual fields and the optic nerve heads. Because posterior subcapsular cataracts are common in patients with RP, miotic therapy may lead to decreased visual acuity.

How Is Glaucoma Associated with Stickler's Syndrome Treated?

The treatment of glaucoma in Stickler's syndrome is mainly medical. The high IOPs respond well to antiglaucoma medications. Miotics should be avoided, as

they may reduce vision in the presence of an axial lens opacity or may induce retinal detachment in these highly susceptible patients.[42]

Future Considerations

What Future Therapies May Be Available for Glaucoma Associated with Retinal Degenerations and Dystrophies?

Gene therapy may alter the course of inherited retinal degenerations and dystrophies. Genetic testing may also help diagnose these conditions earlier.

RHEGMATOGENOUS RETINAL DETACHMENT (SCHWARTZ SYNDROME)

Definition

How Is Glaucoma Associated with Rhegmatogenous Retinal Detachment Defined?

Most patients with a retinal detachment have decreased IOP in the affected eye as compared to their fellow eye. This phenomenon is attributed to increased uveoscleral outflow associated with a retinal break. The magnitude of the decrease is directly proportional to the size of the detachment.[43] Schwartz syndrome refers to unilateral elevation of the IOP associated with retinal detachment.[44]

What Is the Mechanism of Glaucoma in Schwartz Syndrome?

A retinal break allows communication between the subretinal space and the anterior chamber. Photoreceptor outer segments with few inflammatory cells obstruct the trabecular meshwork to cause open-angle glaucoma.[45]

Epidemiology and Importance

How Common Is Glaucoma Associated with Retinal Detachment?

Phelps and Burton[46] examined 817 cases of retinal detachment and found that open-angle glaucoma was present in 4%, and an additional 6.5% had elevated IOP without glaucomatous damage. They also discovered that that 2.1% of 817 patients with retinal detachment had features consistent with Schwartz syndrome.[46]

Diagnosis and Differential Diagnosis

How Is Schwartz Syndrome Diagnosed?

Features of Schwartz syndrome include unilateral elevation of IOP, rhegmatogenous retinal detachment, iridocyclitis, and normalization of the

IOP following retinal detachment repair.[47] The probable etiology of this condition is obstruction of the trabecular meshwork with photoreceptor outer segments.[45]

Treatment and Management

How Is Glaucoma Associated with Schwartz Syndrome Treated?

The management of this condition is aqueous suppression and repair of the retinal detachment. In the majority of cases, glaucoma medications may be discontinued within a few weeks of reattachment of the retina.[48]

Future Considerations

How Have Recent Advancements Contributed to the Treatment of Schwartz Syndrome?

With the advancement of surgical techniques for retinal detachment repair, the reattachment rates for chronic retinal detachments have improved dramatically. In addition, with the advent of vitrectomy for retinal detachment repair, the majority of diffused photoreceptor elements may be removed from the eye at the time of the operation.

CILIOCHOROIDAL EFFUSION (UVEAL EFFUSION SYNDROME)

Definition

How Is Glaucoma Associated with Ciliochoroidal Effusion Defined?

Angle-closure glaucoma is a known complication of ciliochoroidal effusion. These eyes are nanophthalmic and hyperopic due to a short axial length. The sclera in these eyes are thicker than normal and contain unusually disordered collagen fibrils.[49] Uveal effusion may result from either a reduced scleral permeability to proteins or vortex vein compression. Uveal effusion causes forward rotation of the lens-iris diaphragm, inducing angle-closure glaucoma.

Epidemiology and Importance

How Common Is Glaucoma Associated with Uveal Effusion Syndrome?

This syndrome usually occurs in patients with small, hyperopic eyes in the fourth to sixth decades of life. This is a rare condition.

Diagnosis and Differential Diagnosis of the Problem

How Is Glaucoma in Association with Uveal Effusion Syndrome Diagnosed?

In the setting of an elevated IOP, shallow anterior chamber, and narrow angle in a small, hyperopic eye, one should consider angle closure due to cilio-choroidal effusion. These eyes are highly hyperopic due to their short axial length. One should perform a fundus exam to look for a choroidal detachment. An exudative retinal detachment may be observed.

Treatment and Management

The management of glaucoma with uveal effusion syndrome is complex. Angle-closure glaucoma may be treated topically with cycloplegics, aqueous suppressants, and corticosteroids.[50] Miotics may improve some cases but worsen others.[51] Laser iridotomy and peripheral iridoplasty may be tried to eliminate any component of pupillary block. The choroidal effusion is treated with drainage sclerotomies in abnormally thickened sclera.[52,53]

Future Considerations

Future studies may better define the surgical management of these patients. Better diagnostic instruments such as biomicroscopic ultrasonography may help when the diagnosis is not clear.

VITREOUS HEMORRHAGE

Definition

How Is Glaucoma Associated with Vitreous Hemorrhage Defined?

Vitreous hemorrhage may cause glaucoma by three mechanisms: ghost cell glaucoma, hemolytic glaucoma, and hemosiderotic glaucoma.

What Is Ghost Cell Glaucoma?

Campbell et al[54] described a form of glaucoma in which degenerated red blood cells (ghost cells) develop in the vitreous cavity and subsequently enter the anterior chamber where they temporarily obstruct aqueous outflow.

What Is the Mechanism of Ghost Cell Glaucoma?

When red blood cells are present in the vitreous cavity by various mechanisms (trauma, surgery, diabetes, etc.) they degenerate into ghost cells in a matter of weeks. Ghost cells are tan- or khaki-colored, spherical, less pliable structures

that have thin walls and appear hollow except for clumps of denatured hemoglobin, called Heinz bodies. These ghost cells do not readily pass through the trabecular meshwork. Thus, once they gain access into the anterior chamber via a disrupted anterior hyaloid face, they accumulate in the trabecular meshwork and cause elevation of IOP.

What Is Hemolytic Glaucoma?

Hemolytic glaucoma is a condition in which the trabecular meshwork is blocked by hemoglobin-laden macrophages.

What Is Hemosiderotic Glaucoma?

Hemosiderotic glaucoma is a rare type of glaucoma associated with a long-standing vitreous hemorrhage that may lead to trabecular meshwork damage secondary to iron accumulation.

What Is the Etiology of Vitreous Hemorrhage?

The most common causes of spontaneous vitreous hemorrhage are diabetic retinopathy, and retinal break with or without detachment, and retinal vein occlusion.[55,56] Trauma and surgery are commonly associated with vitreous hemorrhage.

Epidemiology and Importance

What Is the Incidence of Glaucoma Associated with Vitreous Hemorrhage?

The incidence of spontaneous vitreous hemorrhage is approximately 7 cases per 100,000 population.[57] The incidence of glaucoma associated with vitreous hemorrhage is not known.

Diagnosis and Differential Diagnosis

How Is Ghost Cell Glaucoma Diagnosed?

Patients with ghost cell glaucoma present with pain, perilimbal injection, and an elevated pressure with a history of a vitreous hemorrhage. There are ghost cells visible in the anterior chamber. Ghost cells are spherical, khaki-colored cell walls of the red blood cell. They are produced 1 to 2 weeks following a vitreous hemorrhage when the red blood cells degenerate. Ghost cells clog the trabecular meshwork because they are less rigid than the normal red blood cell. An anterior chamber paracentesis may be performed to examine the fluid for ghost cells if the diagnosis is uncertain.

How Is Hemolytic Glaucoma Diagnosed?

Hemolytic glaucoma is a condition in which the trabecular meshwork is blocked by hemoglobin-laden macrophages. Because the breakdown of the red

blood cell results in both free hemoglobin and ghost cells, it is likely that ghost cell glaucoma coexists with hemolytic glaucoma.

How Is Hemosiderotic Glaucoma Diagnosed?

Hemosiderotic glaucoma is a rare type of iron-induced glaucoma associated with a long-standing vitreous hemorrhage. Iron released from the hemoglobin of the red blood cell is toxic to ocular structures, which may result in cataract, iris discoloration, and reduced retinal function. Damage to the endothelial cells of the trabecular meshwork results in glaucoma. Most cases of hemosiderotic glaucoma result from iron-containing foreign bodies. The diagnosis is difficult to make clinically.

Treatment and Management

How Is Ghost Cell Glaucoma Treated?

The first step in treating ghost cell glaucoma is to medically reduce the pressure using aqueous suppressants. Topical steroid treatment may reduce inflammation caused by the elevated IOP; however, some authors feel that ghost cell glaucoma is not an inflammatory disease because the primary problem is obstruction of the trabeculum with ghost cells. If medical therapy is not successful, then a thorough vitrectomy is indicated to remove all the ghost cells as well as the remaining vitreous hemorrhage. During vitrectomy, it is important to trim the inferior vitreous base as much as possible, as this location harbors many red blood cells that may continue to produce ghost cells even after vitrectomy.

How Is Hemolytic and Hemosiderotic Glaucoma Managed?

The treatment of hemolytic glaucoma follows the standard medical therapy of glaucoma. If this therapy will be unsuccessful, a paracentesis with irrigation of the anterior chamber may be required.[58]

Treatment of hemosiderotic glaucoma follows the standard therapy of glaucoma as well. Filtering surgery may be required, as permanent damage to the trabecular meshwork may occur.

Future Considerations

What Future Therapies Are there for Glaucoma Associated with Vitreous Hemorrhage?

Experimental nonsurgical treatment options involve improvement of physiologic clearance mechanisms to accelerate fibrinolysis, liquefaction, hemolysis, and phagocytosis.[57]

What Are the Future Concerns About These New Therapies?

There may be an increased incidence of ghost cell glaucoma with the advent of enzymatic vitreolysis of vitreous hemorrhage.

MYOPIA

Definition

How Is Glaucoma Associated with Myopia Defined?

The relative risk of open-angle glaucoma was found to increase sequentially as the level of refractive error studied was shifted away from hyperopia toward higher levels of myopia, becoming three times greater for high myopia as compared to hyperopia.[59] In addition, there is an increased frequency of myopia among patients who have POAG, ocular hypertension, and low-tension glaucoma.[60]

Are Myopes More Susceptible to Glaucoma?

Perkins and Phelps[60] suggested that myopic eyes are more susceptible to the effects of raised IOP than are nonmyopic eyes and that myopes with ocular hypertension have a particularly high risk of the development of field defects. In the Blue Mountains Eye Study, glaucoma was present in 4.2% of eyes with low myopia and 4.4% of eyes with moderate to high myopia compared to 1.5% of eyes without myopia.[61] This study has confirmed a strong relationship between myopia and glaucoma in that myopic subjects had a twofold to threefold increased risk of glaucoma compared to that of nonmyopic subjects. The risk was independent of other glaucoma risk factors and IOP.[61]

What Is the Mechanism of Glaucoma in Myopia?

Nesterov and Katnelson[62] postulated that in myopic eyes, the ciliary body is in a relatively posterior position in relation to the canal of Schlemm so that it has less mechanical advantage in widening the spaces of the trabecular meshwork during accommodation. Tomlinson and Phillips[63] found a statistically significant positive correlation between ocular tension and axial length. They proposed two possible explanations: Either the raised tension is an important factor in producing a large axial length, or the raised tension is produced by a large axial length. Although unlikely in the adult eye, the raised IOP in glaucoma may stretch the globe and cause myopia, especially in congenital and juvenile glaucoma.

The myopic eye tends to have a larger optic cup with a greater cup-to-disc ratio than emmetropic eyes, and it is possible that these anatomic features predispose the disc to pathologic changes from raised IOP.[60] Fluorescein angiographic studies have suggested a reduced choroidal blood flow in myopia,[64] and the amplitude of the ocular pulse is lower in myopes than in emmetropes or hypermetropes.[65,66] The circulation to the optic disc may also be more susceptible to raised IOP.

Epidemiology and Importance

How Common Is Glaucoma in Association with Myopia?

In a population based survey of 2,403 individuals in Israel, increased IOP was observed in high myopes compared to emmetropes and hypermetropes.[67] In

one study, compared with the normal population, the glaucoma population contained about half as many hypermetropic eyes but four times as many myopic eyes.[60] In one series of 68 patients between the ages of 10 and 35 years, myopia was present in 59% of the ocular hypertensives and 73% of the POAG patients.[68] In a population-based study of an Australian white community, the overall glaucoma prevalence was reported to be 3.0%.[69]

Diagnosis and Differential Diagnosis

How Is Myopia Defined?

Myopia, or nearsightedness, is generally classified as axial or refractive. Axial myopia occurs because the eye has a longer axial length, whereas refractive myopia occurs because of the higher refractive properties of the cornea and lens. The vast majority of myopes are axial in nature. In the general population, the prevalence of myopia is approximately 25%.[68]

What Is the Differential Diagnosis for Glaucoma in Association with Myopia?

Friedman[70] showed that an eye of large volume with thin scleral walls will experience greater stress on its scleral walls than a normal eye at the same IOP. During ocular tension measurements, the plunger reading would seemingly indicate a lower IOP in the myopic eye and a higher IOP in the hyperopic eye than actually exists.[70] The optic disc in myopia is larger with a larger cup-to-disc ratio, making evaluation of the optic disc difficult when attempting to make a diagnosis of glaucoma. In addition, tilted discs, which are more common in myopia, may give visual field defects that mimic glaucomatous scotomas. Myopic retinal degeneration is common in patients with high myopia. Myopic retinal degeneration may produce visual field defects that mimic glaucoma.

Treatment and Management

How Is Glaucoma in Association with Myopia Treated?

Because the optic nerve head in myopic eyes may be structurally more susceptible to the effects of raised IOP, appropriate treatment should be initiated once the diagnosis is made.[60,68,71] Similar to patients with POAG, medical therapy should be instituted first and should consist of topical aqueous suppressants and oral carbonic anhydrase inhibitors. Miotics should be avoided due to the higher risk of retinal detachment in these eyes. If the pressure continues to be elevated despite maximal medical therapy, then argon laser trabeculoplasty or filtering surgery should be considered. Young myopic males are also at risk for pigmentary glaucoma, which may respond to peripheral iridotomy.

Because of many confounding variables in making a diagnosis of glaucoma in patients with myopia, factors such as optic disc appearance, visual field, and IOP should be carefully monitored for progression.

Future Considerations

What Are the Future Considerations in Glaucoma in Association with Myopia?

There is ongoing research in finding a genetic link between glaucoma and myopia, which may help us better understand the relationship between these two common disorders.

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◆ 12 ◆

Glaucoma Associated with Ocular Surgery

Eve J. Higginbotham

Definition of the Problem

Based on current teaching regarding glaucoma, glaucoma associated with ocular surgery can be defined as any evidence of optic nerve deterioration and visual field loss that follows either extraocular or intraocular surgery. However, given that such complicated instances have traditionally included problems that occur acutely, prior to the onset of changes in either the optic nerve or visual field, for the purposes of this chapter we will include those instances in which the intraocular pressure (IOP) is simply elevated. However, elevated IOP is simply a risk factor and should not be defined solely in one's definition of glaucoma.

Epidemiology and Importance

Elevated IOP is important to recognize following any surgery given its significant role as a risk factor in some patients as a key "driver" for developing glaucoma. A transient increase in IOP is certainly less worrisome than a 20% or greater sustained increase that may occur in a patient with moderate or severe cupping of the optic nerve. Over time, patients may develop the characteristic changes in the optic nerve and/or the visual field if the unsuspecting clinician fails to closely monitor the patient's course.

There is a range of glaucomas that can follow ocular surgery, from a steroid-induced glaucoma, which may occur following any extraocular or intraocular procedure, to angle closure, which may follow a scleral buckling procedure.

Clinical Pathways in Glaucoma. Edited by Zimmerman and Kooner.
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Because all of these glaucomas are due to another reason, they are considered "secondary." However, these complications, which may follow ocular surgery, can be either open angle or angle closure in nature.

These glaucomas may be further broken down according to a mechanistic classification. The secondary glaucomas can be classified into three subcategories: (1) pretrabecular, (2) trabecular, and (3) posttrabecular. Examples of pretrabecular glaucomas are represented by glaucomas such as neovascular glaucoma, in which a fibrovascular membrane is present, or by the occurrence of epithelial down-growth following a complicated procedure. When red blood cells obstruct the trabecular meshwork, such as ghost cell glaucoma or hemorrhagic glaucoma, the trabecular meshwork becomes the primary factor that contributes to elevated IOP. Sometimes, however, the site of resistance is beyond the trabecular meshwork. When there is an elevation in episcleral venous pressure, as in Sturge-Weber syndrome, or there is a carotid-cavernous fistula, the intraocular pressure can be significantly affected. For those patients who present with a secondary angle-closure glaucoma, one can consider either an anterior or "pulling" mechanism or a posterior or "pushing" mechanism. The anterior secondary angle closure would be typified by neovascular glaucoma or iridocorneal endothelial syndrome. The posterior or pushing mechanism can be further subdivided into pupillary block, such as an intumescent lens, or an elevation in pressure that occurs in the absence of pupillary block, such as ciliary block glaucoma.[1] whichever classification one uses, it is important to recognize and address the underlying cause prior to undertaking aggressive intervention, which can worsen the problem.

What Are the Demographic Characteristics of Patients Who May Develop Glaucoma After Ocular Surgery?

There is no age, gender, race, or ethnic group predilection for any of these glaucomas. However, there are certain ocular characteristics that may make some problems more likely to occur. For example, an eye that may be significantly hyperopic will be more likely to develop malignant glaucoma following laser iridotomy. Similarly, a patient on chronic miotic therapy may also develop malignant glaucoma following filtration surgery. An eye that has evidenced an elevation in IOP prior to cataract surgery would be more likely to develop an elevation in IOP following surgery. Moreover, known steroid responders need careful monitoring in the postoperative period.

What Are the Biological Characteristics of Patients Who May Develop Glaucoma After Ocular Surgery?

There are no biologic characteristics, such as blood levels of antibodies, chemicals, and enzymes, cellular constituents of the blood, and measurements of physiologic functions of different organ systems, that are characteristic for glaucomas associated with ocular surgery.

What Are the Social and Financial Factors of Patients Who May Develop Glaucoma After Ocular Surgery?

Physicians need to assess the patient's ability to pay for the surgical expenses and postoperative medications before undertaking any surgery. Referral to appropriate social agencies and counseling is essential.

What Are the Personal Habits of Patients Who May Develop Glaucoma?

There are no personal habits, such as tobacco or drug abuse, diet, and physical exercise, which are likely to contribute to the development of these glaucomas. Patients who are noncompliant with their medications and those with no family or social support warrant careful postoperative observation.

What Are the Genetic Characteristics of Patients Who May Develop Glaucoma After Ocular Surgery?

A patient who may have a genetic predilection for glaucoma has a higher risk of developing a glaucoma associated with ocular surgery. Any surgical trauma may trigger the condition. See Chapters 1, 2, and 5 for discussions regarding the genetics of these diseases.

Diagnosis and Differential Diagnosis

How Is Glaucoma Associated with Ocular Surgery Diagnosed?

Glaucoma associated with ocular surgery is diagnosed as in other glaucomas. A comprehensive history is necessary, and should include reports of previous trauma, previous reports of elevated pressure, or the ingestion or topical use of steroids or other medications that can confound the clinical picture. A discussion with the referring physician would also be helpful to determine if there were unusual occurrences during prior surgery.

An evaluation of the optic nerve and the visual field are key steps to assessing the level of damage. However, it is important to determine if there are any anatomic changes that can be addressed to alleviate any significant increase in IOP. The ongoing medical or surgical management of the eye will be dependent on the outcome of gonioscopy, disc evaluation, and perimetry.

Can Glaucoma Occur with Any Type of Surgery?

Generally, yes. Patients who undergo even extraocular procedures such as strabismus or refractive surgery can develop steroid-induced glaucoma, for example. Patients who are susceptible may develop an elevation in IOP after 2 weeks or more of continuous use of steroids. It is estimated that 5% of nondiabetic and 20% of diabetics may potentially evidence an increase in IOP.[2] If closely moni-

tored and the patients have not been using topical steroids for a prolonged period of time, then stopping the offending medication will usually result in the IOP returning to baseline.

Generally, patients with preexistent glaucoma may find their condition worsening after ocular surgery. As noted previously, both open-angle and angle-closure glaucomas may be encountered in patients undergoing ocular procedures.

Can Glaucoma Occur Following Laser Procedures?

Yes, there are four laser procedures that will be highlighted here: laser iridotomy, laser photocoagulation, neodymium:yttrium-aluminum-garnet (Nd:YAG) capsulotomy, and laser trabeculoplasty.

A transient increase in IOP may arise following any intraocular procedure. However, since well-tolerated and fast-acting antiglaucoma medications have been introduced, the incidence of pressure elevation following these procedures occurs less often. Consider a series of patients who underwent laser iridotomy described by Lewis and coworkers[3]; 289 eyes of 179 patients underwent peripheral laser iridotomy. Patients' diagnoses were narrow occludable angles, open-angle glaucoma, or chronic angle closure. Patients were treated perioperatively with pilocarpine and apraclonidine. No patients developed an increase in IOP of 25 mm Hg or greater. Only 0.7% of eyes with narrow occludable angles, 0.9% of eyes with open-angle glaucoma, and none of the patients with chronic angle-closure glaucoma developed an IOP elevation of more than 10 mm Hg compared to baseline. Thus, to avoid an increase in IOP in the immediate postoperative period, it is prudent to pretreat with an antiglaucoma medication such as apraclonidine, brimonidine tartrate, dorzolamide, brinzolamide, or pilocarpine. However, if a patient is chronically using an agent, the efficacy may be reduced in the perioperative period. Such reduced efficacy has been noted in patients who were chronically treated with apraclonidine and received this same drug following laser therapy.[4]

Malignant glaucoma or ciliary block glaucoma has been reported following laser iridotomy. This process may be worsened by the use of miotics postoperatively. It has been postulated that some of these eyes may have begun the process of aqueous misdirection prior to the completion of the laser procedure.[5] Bilateral malignant glaucoma has been described in a 50-year-old patient who underwent bilateral laser iridotomies. The patient failed to respond to miotics but did respond to atropine and cyclopentolate. It was postulated that systemic hydrochlorothiazide therapy may have contributed to this presentation.[6] Nevertheless, malignant glaucoma should be suspected if the anterior chamber shallows and the pressure elevates following laser iridotomy.

Another secondary glaucoma that may occur in association with laser iridotomy procedures is pupillary block glaucoma. In uveitic patients, it is common for laser iridotomies to close if there is a significant degree of inflammation. When one completes a laser iridotomy using the argon laser, posterior synechiae can form. Thus, in the presence of a once-patent laser iridotomy now closed, pupillary block can occur. This phenomenon is more likely to occur if pilocarpine is used postoperatively, considering the tendency of this medication to increase inflammation.

Secondary angle closure can occur following panretinal photocoagulation. Intense treatment of the retina can result in choroidal edema and detachment. Subsequently there may be rotation of the ciliary body anteriorly and narrowing of the anterior chamber angle. A patient who may have previously evidenced a narrow angle prior to the laser therapy may perilously slip into angle closure with an associated sustained increase in IOP.

Treatment and Management

How Are the Complications of Malignant Glaucoma and Pupillary Block, Which May Occur Following Laser Iridotomy, Managed?

Malignant or ciliary block glaucoma following laser iridotomy is initially treated with cycloplegic and mydriatic agents, agents that relax the ciliary body enabling its rotation posteriorly, and aqueous suppressants, which reduce the production of aqueous that may become loculated posterior to the vitreous. Essentially the cycloplegic agent paralyzes the circular ciliary muscle fibers and epinephrine tightens the zonules between the ciliary muscle and the lens. Using vitreous dehydrators such as isosorbide 45% at 1.5 cc/kg body weight or intravenous mannitol may assist in eliminating the continued accumulation of fluid in or behind the posterior hyaloid face as well as reduce the pressure of the vitreous body on the anterior segment. Topical antiinflammatory agents should be added to control the inflammation. Peripheral iridoplasty may also be helpful.

Figure 12–1 presents a decision tree that outlines the course of management for malignant glaucoma. Essentially, before one can diagnose ciliary block glaucoma, a patent iridotomy should be present. Otherwise the patient needs to be treated initially for pupillary block glaucoma with the completion of an iridotomy. If there is still a shallow chamber and the IOP is still somewhat elevated, then a choroidal effusion must be ruled out. If there is choroidal effusion, then this patient has angle-closure glaucoma with ciliochoroidal detachment. Cycloplegics and aqueous suppressants should be prescribed and the underlying cause of the ciliochoroidal detachment should be addressed. Argon laser iridoplasty can be tried, or surgical drainage of the choroidal detachment may be required if there is an excessively high IOP or corneal decompensation. However, usually patients will recover with medical therapy over time. If, on the other hand, there is no choroidal effusion, then the eye indeed has developed malignant or ciliary block glaucoma. Medical therapy should be instituted, specifically atropine 1% q.i.d., phenylephrine 10% q.i.d., acetazolamide 250 q.i.d., and a hyperosmotic agent usually b.i.d. This regimen is continued for 4 or 5 days. If this medical regimen is successful then systemic and the mydriatric agents are discontinued.[7] If the problem persists then laser or surgical therapy may be necessary as outlined in Figure 12–1. If the patient is aphakic or pseudophakic, then one can proceed directly to laser or surgical therapy.

If one encounters pupillary block in a uveitic patient following an unsuccessful laser iridotomy procedure, then it is important to reestablish a patent iridotomy. The Nd:YAG laser is less likely to close, and thus completing a laser

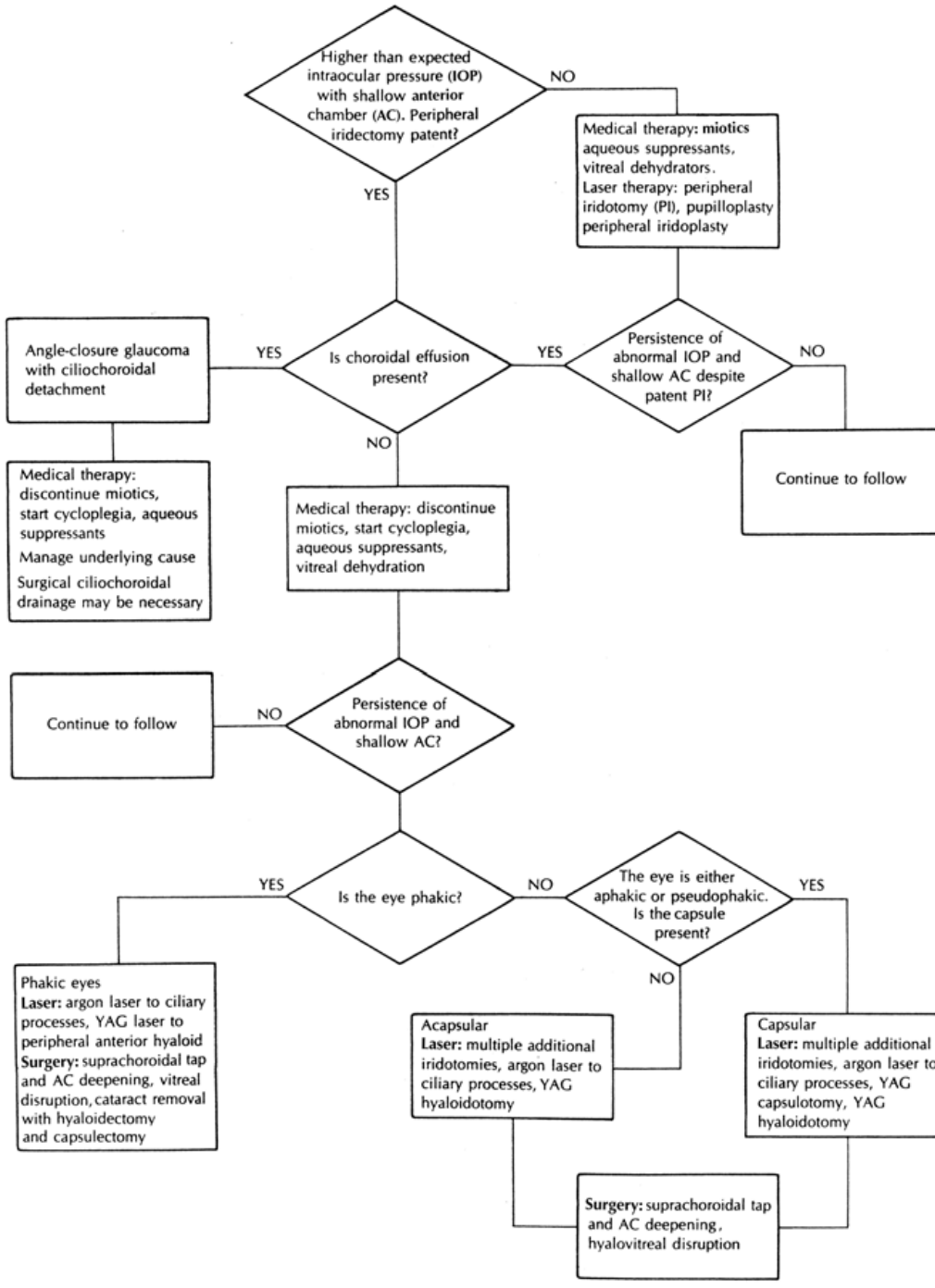

Figure 12–1. Diagnosis and management of malignant glaucoma. (Adapted from Higginbotham EJ, Lee DA (eds): Management of Difficult Glaucoma. Boston: Blackwell Scientific, 1994.)

iridotomy with this laser should be attempted. Intense use of antiinflammatory agents should be considered, and systemic agents may be necessary to overcome the inflammation. Finally, if laser iridotomy is not successful, then a surgical iridectomy should be completed. However, if there is extensive permanent closure of the trabecular meshwork, then a trabeculectomy with adjunctive use of antimetabolites such as mitomycin-C should be performed.

How Are the Complications of Laser Photocoagulation Managed?

This secondary angle-closure problem should be successfully managed by performing laser iridoplasty to deepen the angle recess, initiating cycloplegics to deepen the anterior chamber, and adding topical and systemic antiinflammatory agents. Antiglaucoma medications, particularly aqueous suppressants can be used as needed. Once the inflammatory insult has subsided, the pressure often decreases.

What Is the Etiology of Pressure Elevation Following Nd:YAG Capsulotomy and How Is It Managed?

An increase in IOP may occur following posterior capsulotomy. In a series of 897 Nd:YAG laser posterior capsulotomies, newly diagnosed glaucoma was noted in seven patients (0.78%), and five patients (0.56%) evidenced worsening of preexisting glaucoma.[8]

It is unknown what causes the increase in IOP following Nd:YAG capsulotomy, however, some authors have postulated that small amounts of lens and/or capsular particulates may seriously impair outflow. The Nd:YAG may also cause shock-wave damage to the trabecular meshwork.[9] Patients with preexisting glaucoma are more likely to develop an IOP greater than 30 mm Hg within 1 hour following surgery.[10]

With the advent of α-agonists, the incidence of pressure elevation has markedly decreased. Either apraclonidine 0.5 or 1% or brimonidine tartrate 0.2% can be administered prior to or after the laser procedure, thus blunting the increase in pressure. Topical carbonic anhydrase inhibitors have also been used in this setting. Patients who are already taking an α-agonist have been shown to demonstrate less of an effect when an additional dose is given either before or after laser therapy. If the IOP is sustained, then the medical regimen will need to be adjusted. The frequency of postoperative follow-up of patients is dictated by the level of IOP following the procedure. In most instances, patients are seen in 1 week and then in 4 to 6 weeks.

Interestingly, malignant glaucoma has also been reported following Nd:YAG posterior capsulotomy. A 50-year-old pseudophakic man underwent posterior capsulotomy. The anterior chamber shallowed and the IOP increased. A laser iridotomy failed to lower the IOP. Eventually the patient responded to medical therapy, specifically, atropine, phenylephrine, mannitol, and acetazolamide. The anterior chamber deepened and the IOP decreased.[11]

Is There a Risk of Glaucoma Following Refractive Surgery Procedures?

Steroid-induced glaucoma must always be considered when topical steroids are continued for several weeks. Another potential problem may occur when patients undergo LASIK. During this procedure, sometimes for several seconds, a suction ring is placed on the eye, which elevates the IOP to levels of 60 to 80 mm Hg. Patients with preexisting glaucoma should be cautioned against undergoing this procedure. It is still too early to know if eyes that have undergone this procedure will have long-term problems. However, early results suggest that such a short period of pressure elevation does not significantly harm eyes without glaucoma. All of these patients should be closely monitored. Relying solely on IOP is insufficient because the thickness of the cornea is altered during refractive surgery, and the accuracy of applanation tonometry will be altered. Thus, the examination of the optic nerve and visual field will be even more important in the detection of disease.

Two studies have demonstrated that changes that occur following photorefractive surgery and LASIK decreases the ability to accurately measure IOP. Mardelli and coworkers[12] measured the IOP at baseline and 12 months following photorefractive keratectomy in 111 patients. There was a statistically significant decrease in the mean tonometric measurements in the treated eyes compared to control eyes (0.5 ± 2.1 mm Hg). This difference corresponds to a reduction in corneal thickness, which measured 23 ± 23 microns. LASIK also reduces the accuracy of tonometric measurements. Emara and coworkers[13] documented a mean decrease in the central corneal thickness in 85 eyes of patients who underwent LASIK. The mean central corneal thickness was decreased by 73 μ compared to baseline. The difference between the mean pre- and post-LASIK measurements by applanation was 2.5 mm Hg, which was statistically significant.

Are There Concerns Following Laser Trabeculoplasty?

Elevated IOP can occur following laser trabeculoplasty. In the Glaucoma Laser Trial the acute effects of laser trabeculoplasty was assessed; 271 eyes underwent laser trabeculoplasty as an initial intervention. The IOP rose 5 mm Hg or greater in 34% of patients after one or two sessions; 12% of eyes demonstrated an increase of 10 mm Hg or more.[14] However, a study by Elsas et al[15] failed to demonstrate any long-term effect of pressure spikes on the visual field following trabeculoplasty. Sixty-one patients underwent visual fields 1, 3, and 6 months following laser trabeculoplasty. There were no significant perimetric changes noted. Finally, peripheral anterior synechiae can occur following laser trabeculoplasty; however, synechiae have no adverse effect on the outcome of the procedure.

Can Glaucoma Occur Following Other Procedures?

Yes, glaucoma can occur following cataract surgery, penetrating keratoplasty, scleral buckling procedures, vitrectomy, and even glaucoma surgery. Each of these entities will be discussed in turn.

Are There Specific Types of Patients Who Are at Greater Risk for Developing Glaucoma Following Cataract Surgery Besides Those Patients Who Have a History of Glaucoma?

Yes. Patients with a history of primary open angle glaucoma uveitis, pigmentary dispersion, exfoliation syndromes, a previous history of trauma, or preexisting peripheral anterior synechiae from any cause have a risk of developing an elevation in IOP following cataract surgery[2] (Table 12–1).

What Is the Incidence of an Elevation of IOP Following Cataract Surgery?

The incidence of IOP elevation is dependent on the technique and complexity of surgery and the type of viscoelastic surgery that is used. When extracapsular cataract surgery was more commonly performed, it was estimated that 55% of patients evidenced a pressure elevation of 25 mm Hg or more.[16] The newer techniques of phacoemulsification and smaller incisions have resulted in lower rates of pressure elevation. Clear corneal incisions are associated with a lower risk of pressure elevation.[17] These episodes are often transient; however, patients with moderate or severe glaucomatous disease should be treated prophylactically in the first 24 hours following surgery.

What Are Some of the Reasons Associated with an Increase in IOP Following Cataract Surgery?

There are several ways in which IOP may become elevated following cataract surgery. It is helpful to consider those causes that may be associated with a deep anterior chamber versus a shallow anterior chamber. First, consider a deep anterior chamber. If the incision is made at the corneoscleral limbus, then distortion of the aqueous outflow pathway can contribute to a decrease in out-

Table 12–1. Glaucoma Associated with Cataract Surgery

Presentation:	Elevated intraocular pressure and deep anterior chamber
Causes:	Distorted aqueous outflow pathway due to wound construction
	Inadequate removal of viscoelastic substance
	Pigment dispersion
	Hyphema
	Retained lens material
	Epithelial or fibrous ingrowth
	Choroidal hemorrhage or choroidal effusion
Presentation:	Elevated intraocular pressure and shallow anterior chamber
Causes:	Pupillary block
	Ciliary block or malignant glaucoma
	Iridovitreal block
	Choroidal hemorrhage or choroidal effusion
	Steroid-induced glaucoma

flow facility.[18] Another reason may be that the choice of viscoelastic substance and its incomplete removal from the eye may contribute to an elevation in IOP. Among the currently available substances, such as 1% sodium hyaluronate (Healon), a mixture of 3% sodium hyaluronate (AmVisc), 4% chondroitin sulfate (Viscoat), there is no particular one that causes a pressure elevation more frequently than another. Other causes of elevated IOP following cataract surgery include pigment dispersion, hyphema, and residual lens material and epithelial or fibrous ingrowth. This latter complication is caused by poor wound construction and can be difficult to manage. The diagnosis is made by observing a scalloped border on either the corneal endothelium or the anterior iris surface. One can apply an argon laser burn to the surface and if a fluffy, white lesion occurs, then it is likely epithelium.

If the patient presents with a shallow chamber and elevation of IOP, then the differential is as follows: pupillary block, iridovitreal block, malignant glaucoma or ciliary block glaucoma, and choroidal effusion or hemorrhage. Pupillary block occurs more commonly in the setting of an anterior chamber lens implant and less commonly with posterior chamber lens implants. Iridovitreal block may occur if the anterior hyaloid face is adherent to the posterior iris, thus limiting the egress of fluid from the posterior chamber.[19] Malignant glaucoma is characterized by entrapment of aqueous in the vitreous cavity or posterior to the posterior hyaloid face and can also present as a shallow anterior chamber and elevated IOP. Finally, if the patient reports severe pain and decreased vision, then choroidal hemorrhage must be considered. This complication may occur more commonly in patients who are high myopes, in patients with previously inflamed eyes, or in elderly patients who have undergone previous vitreous surgery, in particular. The surgical management of these complications will be discussed in Chapter 11.

How Is Glaucoma Associated with Cataract Surgery Managed?

For those patients who may simply evidence a transient increase in IOP, one can initiate antiglaucoma medications as needed. Intracameral acetylcholine (Miochol) and carbachol (Miostat) can effectively lower IOP.[20] Postoperatively, if a problem persists, adrenergic antagonists, α-agonists, and topical carbonic anhydrase inhibitors may be considered as potential agents that can be used. Generally it may take up to 72 hours for the pressure to return to baseline if absolutely no viscoelastic substance was removed from the eye. Latanoprost may be considered if other drugs are not effective. Antiinflammatory drugs should be used, particularly in those instances in which residual lens material is present. If the IOP elevation persists beyond the immediate postoperative period, then the patient should be monitored by undergoing serial visual fields and close observation of the optic nerve. Laser trabeculoplasty may be a consideration for those patients who are not controlled with antiglaucoma medications, once the eye has healed and is quiet.[21] The success among pseudophakic patients is approximately 50% following laser trabeculoplasty. If vitreous is present in the anterior chamber, laser trabeculoplasty should not be performed.[22]

For those patients who present with fibrous or epithelial down-growth, once the extent of the down-growth has been assessed with the assistance of the argon laser, then the involved iris can be removed. If the corneal endothelium is involved, then cryotherapy can be performed.

If there is a shallow chamber and an elevation in IOP, then one should consider the differential considered above. If there is evidence of a choroidal effusion or hemorrhage, and if the IOP is excessively elevated, then one may consider drainage of the hemorrhage. Otherwise, antiglaucoma medications (excluding parasympathomimetics and latanoprost) should be used. Over time choroidals will resorb; however, sometimes the medications may be insufficient to control the secondary pressure elevation, particularly in an eye with severe glaucoma, and surgical intervention may be necessary.

If the peripheral iridectomy is not patent or present, then a peripheral iridotomy should be performed. If iridovitreal block is suspected, then the anterior hyaloid, which may be visible through the iridotomy, should be treated using the Nd:YAG laser. If malignant glaucoma is suspected, then Nd:YAG laser applications into the vitreous may be necessary as well as the completion of an Nd:YAG capsulotomy. Immediate deepening of the anterior chamber is usually observed if vitreolysis is successful in releasing trapped aqueous.

In any case, if initial attempts to control the pressure either medically or using specific laser procedures are not successful, then filtration surgery should be performed. Because these patients have undergone previous surgery, an antifibrotic agent should be used adjunctively.

What Types of Glaucoma Occur Following Penetrating Keratoplasty?

As in glaucoma following cataract surgery, there are several causes of elevated IOP and glaucoma following penetrating keratoplasty. These entities include distortion of the aqueous outflow pathway, angle-closure glaucoma, steroid-induced glaucoma, and worsening of preexisting glaucoma.[2] Each of these entities will be considered in turn (Table 12–2).

Table 12–2. Glaucoma Associated with Penetrating Keratoplasty

Trabecular meshwork collapse
Tight and mid-stromal suturing
Loss of trabecular support
Distorted angle by same-sized corneal buttons
Angle-closure glaucoma with peripheral anterior synechiae formation
Pupillary block
Chronic uveitis
Choroidal detachment with ciliary body rotation
Ciliary block or malignant glaucoma
Steroid-induced glaucoma
Worsening of preexisting glaucoma

Adapted from Higginbotham EJ, Lee DA (eds): Management of Difficult Glaucoma. Boston: Blackwell Scientific, 1994.

What Are the Causes of the Distorted Anatomic Changes in the Aqueous Outflow Pathway?

Tight incision closure and employing a donor button that is the same size are two causes that have been implicated. Campbell and Grant[23] experimentally sutured corneas without making incisions; when sutures were tightly knotted, there was an increase in outflow facility and collapse of the trabecular meshwork. This problem rarely occurs in phakic patients and has been reported to occur in as many as 70% of aphakic eyes.[24] Apparently without the countersupport of the natural lens, the trabecular meshwork fails to maintain its normal anatomy. It is unclear if a pseudophakos provides sufficient counterbalance. Finally, same-size donor buttons have been implicated, as well, in distorting the angle, thus leading to an elevation in IOP.[25]

What Types of Angle-Closure Glaucoma Can Occur?

As occurs following cataract surgery, pupillary block and malignant glaucoma can occur in these cases, too. Even in the absence of pupillary block, the eye can experience closure due to peripheral anterior synechiae formation, which may be due to hypotony, a flaccid iris that becomes adherent, or uveitis.

What Are Some Additional Reasons for Either Elevated IOP or Glaucoma Occurring Postoperatively?

Steroid-induced glaucoma likely occurs more commonly than suspected, given the necessary frequent use of potent steroids following postpenetrating keratoplasty. The need for long-term use of these drugs contributes to the likelihood of this problem occurring.[26] Moreover, as stated earlier, if a patient has preexisting glaucoma, then it is likely that the glaucoma will worsen if one does not take the necessary precautions to avoid IOP elevation.

How Is Elevated IOP or Glaucoma Following Penetrating Keratoplasty Managed?

There is little one can do to primarily correct the distortion of the trabecular meshwork. However, one can begin antiglaucoma medications early on, primarily aqueous suppressants. Miotics and prostaglandin analogues should be avoided due to the propensity of these agents to enhance inflammation in some eyes. Alpha-agonists may be considered as either a first-line or second-line class of drugs. The question of whether one should use a topical carbonic anhydrase inhibitor is an interesting one given the presence of carbonic anhydrase II in the corneal endothelium. It is probably wise not to use the topical agent in the acute or subacute period, but use the systemic agents instead. Considering that the corneal endothelium has carbonic anhydrase isoenzyme II as an important cellular component, the application of a topical carbonic anhydrase inhibitor may affect the ability of these endothelial cells to function. Generally, one should consider using through-and-through sutures and a oversized donor graft to decrease the chances of distorting the trabecular meshwork.

If there is evidence of pupillary block, then it is important to complete a laser iridotomy, preferably with a Nd:YAG laser. If there is extensive peripheral anterior synechiae formation, laser gonioplasty or iridoplasty can be performed. However, a clear corneal graft is necessary to visualize the angle. These techniques are more successful if they are performed within the first year of surgery.

For patients who evidence malignant glaucoma, treatment begins with medical therapy first, particularly in phakic patients. In pseudophakic and aphakic patients, there is the advantage of being able to proceed directly to the application of the Nd:YAG laser to the anterior hyaloid face and, if necessary, into the vitreous.

The management of steroid-induced glaucoma can be a little tricky in this setting, given the need to continue potent steroids to avoid graft rejection. It is more important to keep the inflammation controlled rather than shift to less potent steroids. There are steroids, however, that claim similar potency to Pred forte 1% (prednisolone acetate 1%) but do not elevate IOP. Vexol 1% (Rimexolone 1%) and Lotemax 0.5% (Loteprednol 0.5%) are examples of such steroid formulations and thus may be tried in this setting. Nevertheless, antiglaucoma medications can be initiated.

If there is significant visual field deterioration, optic nerve change or anticipated changes in either parameter in the presence of a sustained increase in IOP, then surgery may be necessary. If the angle is open and there is no previous history of laser trabeculoplasty, then this procedure can be performed. Van Meter and coworkers[27] noted a 80% success of argon laser trabeculoplasty in aphakic and pseudophakic eyes following keratoplasty. Other options include a trabeculectomy with adjunctive use of antifibrotic agents, implantation of a glaucoma filtration device, or laser cycloablation. A summary of the above-discussed approach to the management of patients postkeratoplasty is highlighted in Figure 12–2.

What Types of Glaucoma Are Noted Following Retinal Surgery?

Three retinal procedures are considered here: (1) scleral buckling procedures, (2) pars plana vitrectomy, and (3) intraocular gas or silicone oil (Table 12–3).

What Causes Glaucoma Following Scleral Buckling Procedures?

When a snug scleral buckle is applied, there is blockage of the vortex veins, which leads to increased transmural pressure in the capillaries of the ciliary processes and marked distention of the ciliary body vasculature. As the ciliary body swells, it rotates anteriorly and pushes the iris root into the angle. This mechanism has been confirmed experimentally.[28,29] Pavlin and coworkers[30] documented supraciliary effusions and ciliary body thickening in 15 patients 1 week following scleral buckling procedures using ultrasound biomicroscopy. Supraciliary fluid was noted in 80% of patients. The thickness of the ciliary body increased on average 0.15 $\pm$ 0.1 mm, and 55% of the patients evidenced anterior bowing of the iris. In three patients, the angle closed in one to three

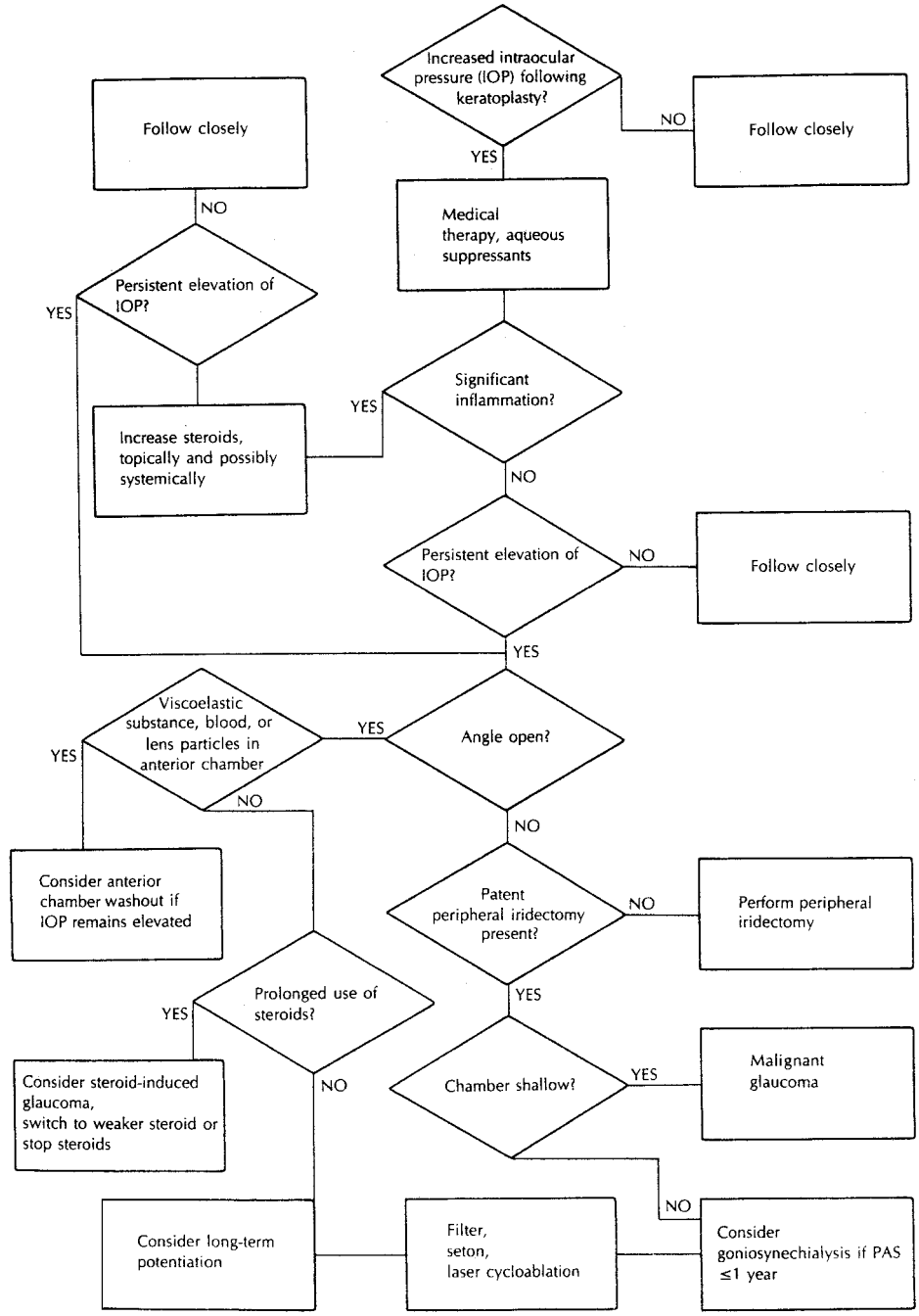

Figure 12–2. Management of the patient with postpenetrating keratoplasty-associated glaucoma. (Adapted from Higginbotham EJ, Lee DA (eds): Management of Difficult Glaucoma. Boston: Blackwell Scientific, 1994.)

Table 12–3. Glaucoma Associated with Retinal Surgery

Procedure:	Scleral buckling procedure
Glaucomas:	Angle closure secondary to anterior rotation of the ciliary body
	Anteriorly placed buckle
Procedure:	Pars plana vitrectomy
Glaucomas:	Hyphema
	Ghost cell glaucoma
	Retained lens material
	Neovascular glaucoma
	Angle recession glaucoma
Procedure:	Intraocular gas and silicone oil
Glaucomas:	Pupillary block glaucoma
	Ciliary block or malignant glaucoma
	Trabecular meshwork obstruction secondary to silicone oil
	Steroid-induced glaucoma.
	Preexisting glaucoma

quadrants. In spite of these anatomic changes, none of these patients developed complete angle closure or glaucoma. Another reason may be linked to a scleral buckle that is positioned too anteriorly.

What Causes Glaucoma Following Pars Plana Vitrectomy?

There are a variety of reasons why pars plana vitrectomy may result in glaucoma. Oftentimes, the reasons why one may decide to perform the pars plana vitrectomy may be linked to the causes of glaucoma following the procedure. First, consider blood in the anterior chamber. If there was a vitreous hemorrhage either pre- or postoperatively, then ghost cell glaucoma may develop 10 to 14 days following a fresh bleed. One may observe a layer of khaki-colored cells in the anterior chamber. Second, if a lensectomy was performed at the same time as a vitrectomy, then retained lens material may be present. Third, consider a diabetic patient who may have undergone a pars plana vitrectomy due to proliferative disease. It is not unusual to see iris and angle neovascularization occur prior to or following the procedure. Fourth, steroid-induced glaucoma is another important consideration in this setting as well as preexisting glaucoma. Finally, trauma can result in significant damage to not only the posterior segment but also the trabecular meshwork. Thus, signs of angle recession may be observed on gonioscopy.[31]

Malignant glaucoma has also been reported following vitrectomy. A 65-year-old without a previous history of malignant glaucoma developed aqueous misdirection following pars plana vitrectomy, scleral buckle, and extracapsular cataract extraction with posterior chamber intraocular lens implantation, despite medical therapy, Nd:YAG laser capsulo-hyaloidotomy, and surgical disruption of the anterior hyaloid face. The patient's condition resolved after a repeat vitrectomy, which included hyaloido-capsulo-iridectomy.[32] Thus, the management of ciliary block glaucoma can be challenging.

Because Intraocular Gas and Silicone Oil Are Placed in the Posterior Segment, How Can These Surgical Adjuncts Cause Problems in the Anterior Segment?

Intraocular pressure can increase within the eye if the intraocular gas bubble expands. If the patient is required to lie in a prone position, then blood and fibrin can clog the trabecular meshwork directly.[33] On the other hand, if the patient is allowed to lie on his or her back, then the anterior chamber can shallow and obstruct egress of aqueous from the anterior chamber. Pupillary block can occur if the flow of fluid from the posterior segment to the anterior segment has been completely blocked.[34]

When silicone oil begins to emulsify, small bubbles can block the trabecular meshwork.[35] Histologically, obstruction of the trabecular meshwork has been noted due to small silicone bubbles, pigmented cells, and silicone-laden macrophages.[36] Higher viscosity silicone oil, the use of 5,000 centistokes, has been noted to result in fewer emulsified silicone droplets in the anterior chamber and a lower risk of glaucoma.[36]

Henderer et al[37] of the Bascom Palmer Eye Institute in Miami, Florida, assessed the risk factors for the development of sustained IOP in a series of 532 patients who underwent silicone oil injection for the management of complex retinal detachments. Patients were further subdivided into two groups—those with and without cytomegalovirus. Among those patients with cytomegalovirus, 10% had hypotony by 6 months. By 1 year, 5.9% evidenced an elevation in IOP and 10% were noted to be hypotonous. On the other hand, among those patients without cytomegalovirus, 12.9% had an elevated IOP and 14.1% developed hypotony by 6 months. At 1 year, there were 21% of patients with an elevation in IOP and 27.3% evidenced hypotony. Risk factors for an elevation in IOP include previously diagnosed glaucoma, diabetes mellitus, and an already-high IOP.

How Are Such Difficult Glaucomas Managed?

One's initial approach should be medical management, beginning with adrenergic antagonists and topical carbonic anhydrase inhibitors. Depending on the magnitude of the pressure elevation, then systemic carbonic anhydrase inhibitors may be required. Acetazolamide 250 mg q.i.d. will often control the pressure more consistently than the sequels in this acute period. It may be necessary in these acutely inflamed eyes to use topical steroids and even systemic steroids.

If there is pupillary block due to a gas bubble, for example, then a laser iridotomy should be performed. In the setting of silicone oil and pupillary block, an inferior laser iridotomy should be performed. If there is anterior rotation of the ciliary body due to a tight buckle, then peripheral iridoplasty or gonioplasty should be attempted. In those patients in whom the silicone oil is a problem, laser cycloablation may be the first choice. If the silicone oil is fairly compartmentalized, consider a filtration device.

Evidence of ghost cell glaucoma would suggest the need to wash out the anterior chamber. Similarly, retained lens material that is problematic should be removed. In patients who chronically have an increase in IOP and loss or antic-

ipated loss of field or neuroretinal rim deterioration of the optic nerve, trabeculectomy with an antifibrotic agent or filtration device should be considered.

It may be necessary to remove some of the intraocular gas if the IOP is excessively elevated. IOP elevation has been associated with central retinal vein occlusion.[33] A summary of the treatment of patients following retinal surgery is shown in Figure 12–3.

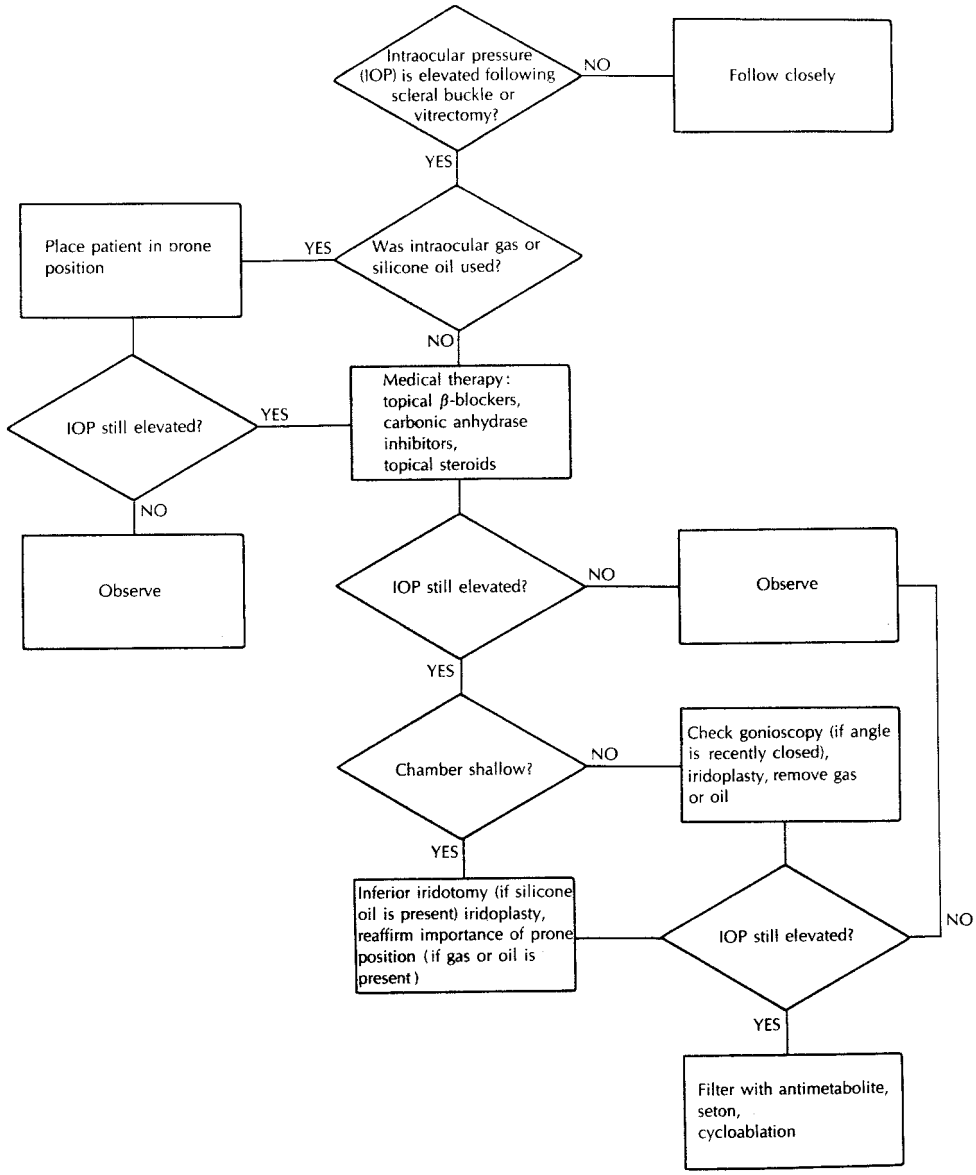

Figure 12–3. Management of the patient after vitrectomy and scleral buckle. (Adapted from Higginbotham EJ, Lee DA (eds): Management of Difficult Glaucoma. Boston: Blackwell Scientific, 1994.)

Even Following Glaucoma Surgery, Can There Be a Sustained Increase in IOP?

Yes, any time the eye is mechanically changed, there can be an undesirable outcome. Consider the possibilities of a sustained increased in IOP following trabeculectomy, glaucoma filtration device surgery, and laser cycloablation.

In a trabeculectomy, if the anterior chamber is deep and the pressure is high, one must consider the following: (1) blocked sclerostomy, (2) tight flap sutures, (3) choroidal effusion or hemorrhage, (4) steroid responder, (5) Tenon's cyst or encapsulated bleb, (6) failed bleb, or (7) endophthalmitis. If the anterior chamber is shallow and the IOP is elevated, then consider the following: (1) pupillary block glaucoma, (2) malignant or ciliary block glaucoma, or (3) choroidal effusion or hemorrhage. The management of these entities is covered in other chapters.

When glaucoma filtration devices are used, there is a hypertensive phase that occurs 3 to 4 weeks following surgery, after which the IOP decreases. However, over time there may be a steady increase in pressure, which will require the initiation of antiglaucoma medications or potentially additional surgery. Entities to consider if faced with a sustained increase in IOP include the following: (1) blocked tube, (2) encapsulated bleb, and (3) steroid responder.

Finally, with regard to cycloablation the following scenarios should be considered: (1) inadequate treatment or (2) steroid responder.

Future Considerations

With the advent of newer techniques for performing cataract surgery, the risks of sustained elevation in IOP will continue to diminish over time. Smaller incisions and less reliance on viscoelastic substances throughout the procedure will minimize the distortion of the anatomy of the globe. Preventive measures such as pupilloplasty and larger donor grafts for avoiding glaucoma following penetrating keratoplasty are commonly employed. The introduction of valved filtration devices, which are easier to insert and manage postoperatively, facilitate one's ability to control those patients who were once considered refractory to treatment.

There are new antiglaucoma medications, including combination drugs such as CoSopt (combination of timolol maleate and dorzolamide hydrochloride), and a drug which combines latanaprost and timolol. Medications on the horizon such as hypotensive topical lipids, new prostaglandin analogues, and neuroprotective agents such as systemic memantine will also provide additional therapeutic options for our patients.

Antifibrotic agents such as mitomycin-C and 5-fluorouracil have changed the number of patients who are now successfully filtered; future agents, however, which include antibodies to cytokines and growth hormones, may cause less hypotony than what is generally seen with these current agents. There have been many advances in ocular surgery that have improved the outcomes of our patients. There are still many more advances we can expect in the future.

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◆ 13 ◆

Traumatic Glaucoma

Mohamed-Sameh H. El Agha

Definition

How Is Traumatic Glaucoma Defined?

Traumatic glaucoma is the occurrence of elevated intraocular pressure (IOP) secondary to ocular trauma. However, not every posttraumatic IOP elevation is necessarily due to trauma; for instance, the eye may have harbored primary glaucoma prior to the trauma. Furthermore, traumatic glaucoma may be masked by coincidental pathology that lowers the IOP. Table 13–1 shows how the IOP level may be interpreted following trauma.

Table 13–2 lists the different types of trauma that may be sustained by the eye. Glaucoma complicating intraocular surgery is discussed in Chapter 12. Head injury may lead to a carotid-cavernous fistula, which may give rise to glaucoma

Table 13–1. Interpretation of Intraocular Pressure (IOP) Level Following Trauma

High IOP
Preexisting primary glaucoma*
Preexisting primary glaucoma + traumatic glaucoma*
Pure traumatic glaucoma
Low IOP
Missed rupture globe (e.g., posterior scleral rupture)
Cyclodialysis
Ciliary shutdown
Choroidal effusion
Retinal detachment
Normal IOP
No ocular damage leading to glaucoma
Combination of high and low IOP

*The fellow eye may show manifestations of primary glaucoma.

Clinical Pathways in Glaucoma. Edited by Zimmerman and Kooner.
Thieme Medical Publishers, Inc., New York © 2001.

Table 13–2. Types of Ocular Trauma

Mechanical injury
Direct
Nonpenetrating (blunt) trauma
Penetrating trauma (± intraocular foreign body)
Surgical trauma
Cataract surgey
Glaucoma surgery (incisional and laser)
Penetrating keratoplasty
Scleral buckling
Pars plana vitrectomy
Nd:YAG laser surgery
Indirect
Head injury
Chemical injury
Alkali burns
Acid burns
Radiation injury
Electrical injury
Thermal injury

Nd:YAG, neodymium:yttrium-aluminum-garnet.

by raising episcleral venous pressure; this is discussed in Chapter 6. Otherwise, all other forms of traumatic glaucoma are discussed in detail in this chapter.

What Are the Mechanisms of Traumatic Glaucoma?

Much like primary glaucoma, traumatic glaucoma may be of the open-angle or closed-angle type. In open-angle varieties, the obstruction to aqueous outflow may be pretrabecular (e.g., epithelial down-growth), trabecular (e.g., glaucoma complicating hyphema, and ghost cell glaucoma), or posttrabecular (e.g., elevated episcleral venous pressure secondary to a carotid-cavernous fistula). Angle closure results from apposition or adherence of peripheral iris to the trabecular meshwork or peripheral cornea. In the anterior ("pull") mechanism, an abnormal tissue in the angle contracts and pulls the iris into the angle (e.g., a fibrovascular membrane associated with neovascular glaucoma). Posterior ("push") mechanisms include pupillary block (e.g., by a swollen cataractous lens) and forward movement of the iris-lens diaphragm (secondary to ciliochoroidal effusion or ciliary block).

How Long After Trauma Does the IOP Rise Occur?

Depending on pathogenesis, the onset of IOP elevation following trauma is variable. The IOP may rise in the first few hours following trauma, as in hyphema. Lens particle glaucoma, for example, will only appear a few days after penetrating trauma. Ghost cell glaucoma requires at least 2 weeks to develop. Angle recession glaucoma typically develops years after the traumatic incident. Therefore, a patient presenting with traumatic glaucoma may have even forgotten the traumatic incident that caused the IOP elevation. The

temporal aspect of the different types of traumatic glaucoma will be discussed under each category.

In this chapter, traumatic glaucoma will be discussed under the following categories: nonpenetrating trauma, penetrating trauma, chemical injury, radiation injury, electrical injury, and thermal injury. Figure 13–1 shows the general lines of management of traumatic glaucoma.

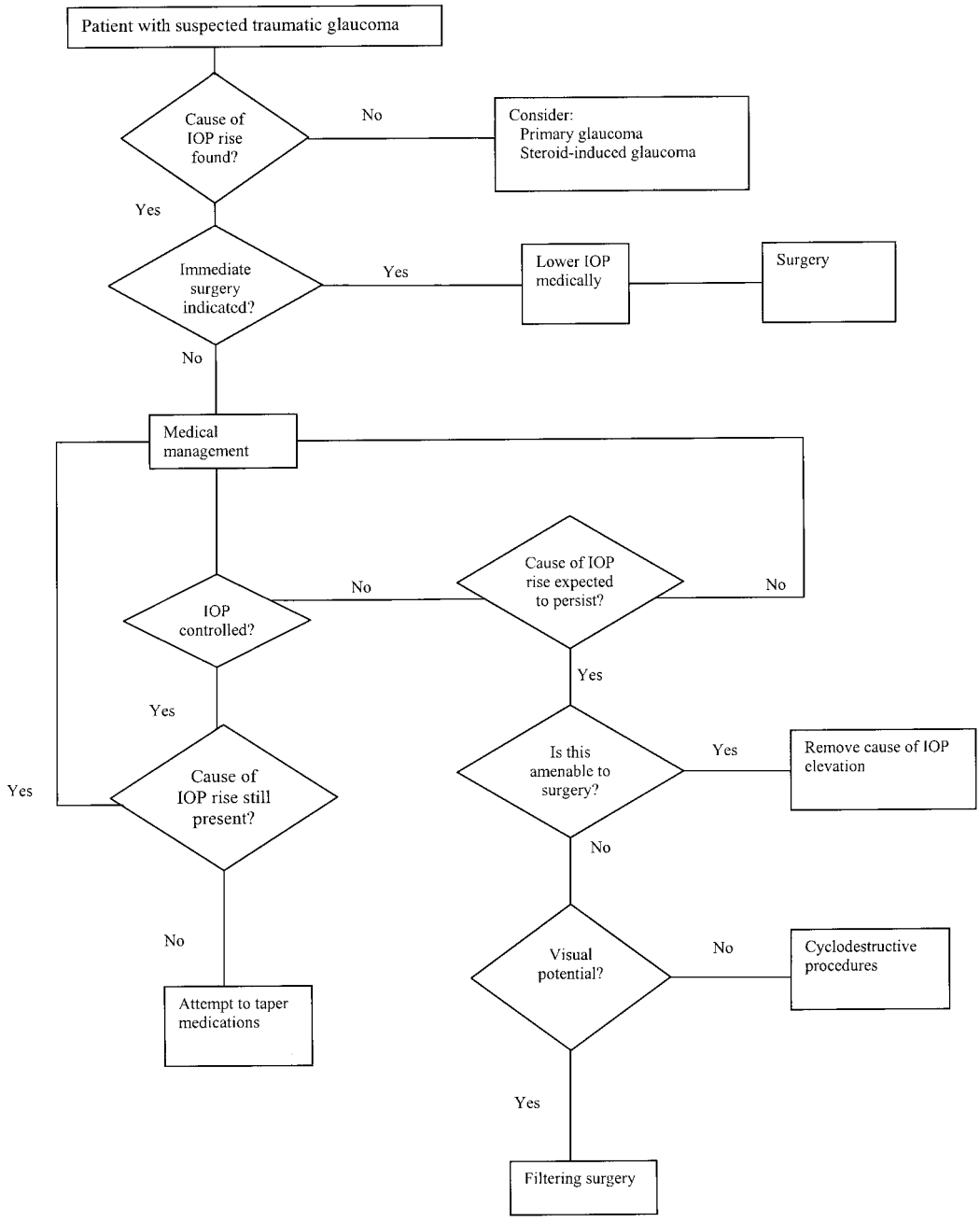

Figure 13–1. General lines of management of traumatic glaucoma.

GLAUCOMA COMPLICATING NONPENETRATING TRAUMA

Definition

How Is the Problem Defined?

Nonpenetrating ocular trauma is injury to the eye resulting from impact of a blunt injurious agent that does not penetrate the globe. Whether or not the trauma is penetrating depends on the size, shape, weight, composition, speed, and direction of the injuring object, as well as the impact, location, and the status of the eye and ocular adnexa before the injury. Various types of glaucoma may complicate nonpenetrating ocular trauma.

Epidemiology and Importance

What Type of Patient Is More Liable to Sustain Direct Ocular Trauma?

Most patients sustaining direct ocular trauma—whether penetrating or blunt—are young, typically less than 30 years of age.[1–7] The setting of ocular trauma is related to age, play being the most common in children, sports and assaults in young adults, and work and domestic accidents in older adults.[8–10] Males are more commonly victims of ocular trauma than females.[2,7,11,12] Patients from lower socioeconomic groups experience more severe and frequent ocular trauma.[12]

Diagnosis and Differential Diagnosis

What Is the Differential Diagnosis of Glaucoma Secondary to Nonpenetrating Trauma?

Table 13–3 lists the various types of glaucoma complicating nonpenetrating trauma. These may occur singly or in combination. For example, hyphema may be associated with lens dislocation and trabecular injury. Figure 13–2 shows the differential diagnosis of elevated IOP in the presence of recent blunt trauma, and Figure 13–3 after an old traumatic incident.

Table 13–3. Types of Glaucoma Associated with Nonpenetrating Trauma

Glaucoma secondary to hyphema
Hemolytic glaucoma
Hemosiderotic glaucoma
Ghost cell glaucoma
Angle recession glaucoma
Glaucoma secondary to trabecular injury
Glaucoma secondary to traumatic cataract
Glaucoma secondary to lens dislocation
Glaucoma secondary to forward movement of the iris-lens diaphragm
Glaucoma secondary to posttraumatic uveitis

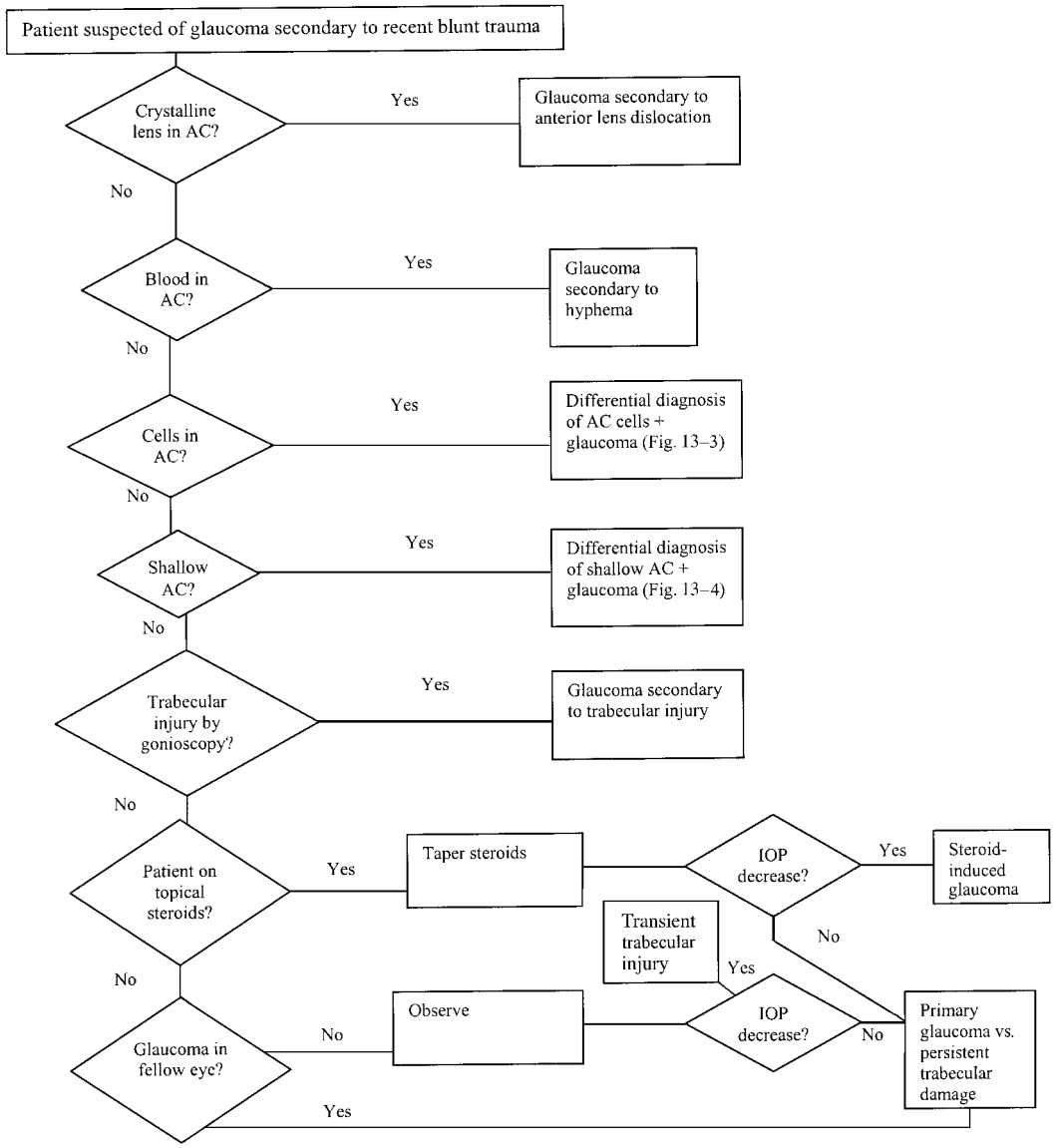

Figure 13–2. High IOP in the presence of recent blunt trauma.

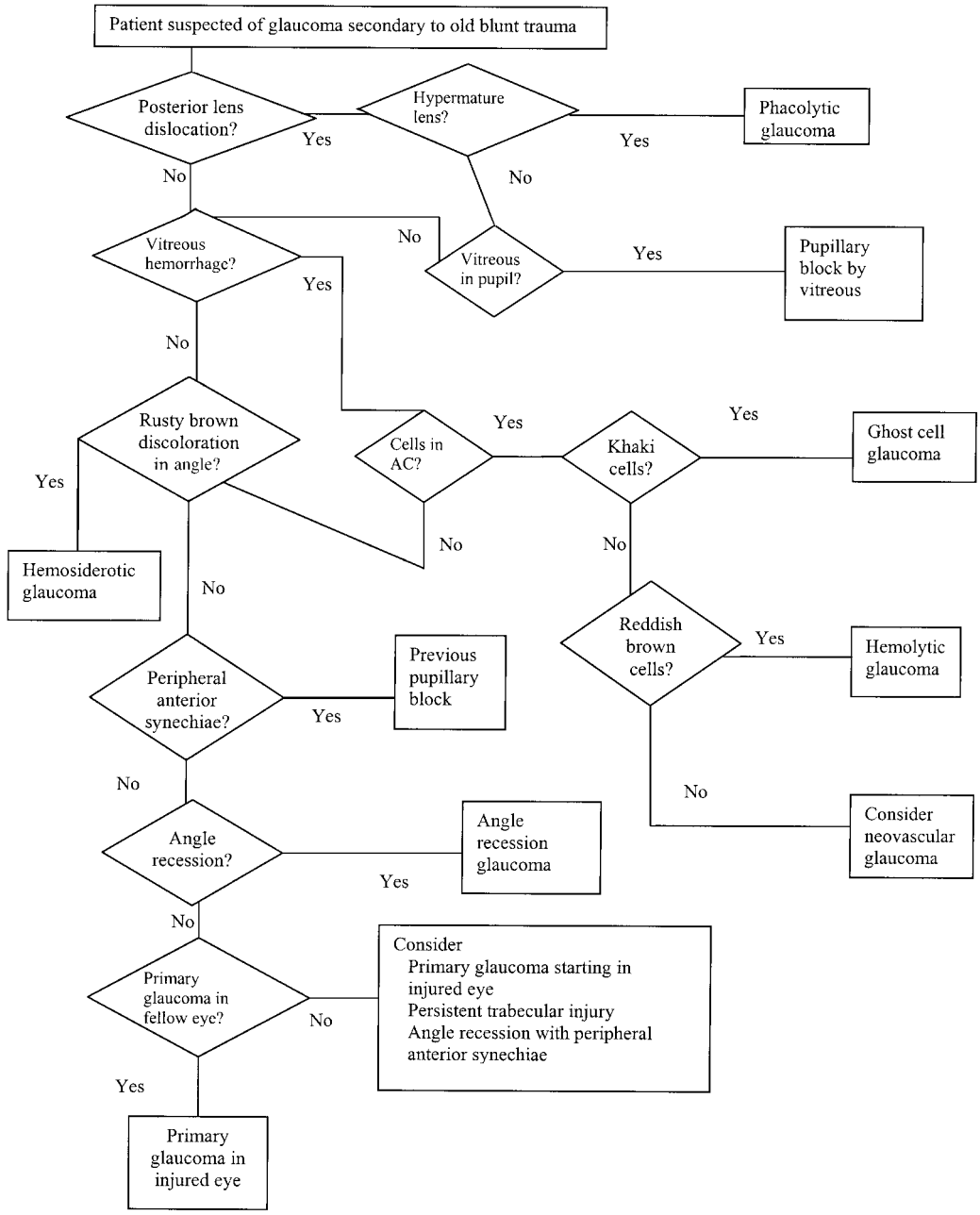

Figure 13–3. IOP elevation in the presence of old blunt trauma.

Treatment and Management

How Is Glaucoma Secondary To Nonpenetrating Trauma Managed?

In most cases, initial management of glaucoma is lowering of IOP through aqueous suppressants, such as beta-lockers, α_2-agonists, and carbonic anhydrase inhibitors (CAIs), and, if necessary, hyperosmotic agents such as mannitol. Definitive management depends on the cause, as is discussed below.

In the following section, each of the different types of glaucoma complicating nonpenetrating ocular trauma (listed in Table 13–3) is discussed in detail.

Glaucoma Complicating Hyphema

Definition

How Is Glaucoma Complicating Hyphema Defined?

Hyphema is characterized by red blood cells in the anterior chamber and is frequently associated with glaucoma. Traumatic hyphema occurs most often from a tear in the anterior surface of the ciliary body, with resultant disruption of the major arterial circle of the iris, arterial branches to the ciliary body, or veins coursing between the ciliary body and the episcleral venous plexus. In most cases, the blood clears within a few days by egress through the trabecular meshwork. If the hyphema persists, an additional problem, such as trabecular meshwork injury, uveitis, vitreous hemorrhage, or rebleeding, must be suspected.[13]

What Are the Mechanisms Underlying Glaucoma Complicating Hyphema?

There are several mechanisms by which hyphema may elevate the IOP. Most frequently, there is mechanical obstruction of the trabecular meshwork by erythrocytes and blood products. In cases with larger hyphemas, pupillary block by a blood clot may also contribute to the elevated IOP.[14] Because fresh erythrocytes easily pass through the normal conventional aqueous outflow system, it is presumed that the IOP rises as a result of temporary impairment of trabecular meshwork function following blunt trauma. Even assuming normal outflow facility, the trabecular meshwork may be overwhelmed transiently by the numbers of red blood cells, combined with plasma, fibrin, and debris.[13]

Typically, IOP elevation is transient, subsequently falling to a mildly subnormal level for a few days.[15] Persistent glaucoma is a rare complication. In a retrospective study of 314 patients with hyphema, Kearns[16] reported a 1% incidence of persistent glaucoma.

Epidemiology and Importance

What are the Risk Factors for Glaucoma Complicating Hyphema?

Hyphema is a frequent sequela of nonpenetrating (and penetrating) trauma. The incidence varies in different reports, ranging from 6% in a study of pediatric

ocular trauma[12] to 55.2% in a survey of penetrating injuries caused by assault.[3] Patients with traumatic hyphema are most often young males, with sports-related injuries and assaults accounting for the majority of cases associated with blunt trauma.[16]

The incidence of elevated IOP in traumatic hyphema has been found to correlate well with the size of the hemorrhage. Coles[17] studied 235 cases of traumatic hyphema, and found elevated IOP in 13.5% of eyes with hyphema filling less than half of the anterior chamber, 27% with hyphema filling more than half of the anterior chamber, and 52% with total hyphema. Elevated IOP is also more commonly seen in eyes that rebleed. In a series of 113 cases, glaucoma developed in 33% of patients who rebled and in 100% of patients when rebleeding resulted in eight-ball hyphemas.[18]

Patients with sickle cell hemoglobinopathy may have IOP elevation disproportionate to the amount of the hyphema.[19] Their erythrocytes have a tendency to sickle in aqueous humor, and the sickled cells may pass slowly through the trabecular meshwork. These patients are also in greater jeopardy from the elevated IOP because of their predisposition to central retinal artery occlusion.[19,20]

Diabetes mellitus has also been implicated with delayed clearance of erythrocytes from the anterior chamber, as erythrocytes from patients with proliferative diabetic retinopathy show decreased deformability and increased adherence.[21]

Diagnosis and Differential Diagnosis

How Is Hyphema Diagnosed?

The clinical diagnosis of hyphema is based on the finding of red blood cells in the anterior chamber. The amount varies from rare circulating cells in the aqueous to subtotal hyphema with a level, or even total hyphema that may darken to become a "black-ball" or "eight-ball" hyphema. The presence of uniformly bright red blood indicates a fresh hemorrhage, although this may darken with time. The presence of layering (i.e., a mixture of fresh and clotted blood) should alert the examiner to the possibility of rebleeding.[13]

Once hyphema is detected, it should not be immediately assumed that the trauma was blunt. Penetrating trauma, with or without an intraocular foreign body, may also cause hyphema. Therefore, the examiner should reascertain the nature of the injury from the patient, or the accompanying family members. The eyelids, conjunctiva, cornea, and sclera should be carefully examined with the slit lamp for the possibility of penetrating injury. If necessary, plain x-ray and computed tomography (CT) imaging may be performed to exclude intraocular foreign bodies. These imaging techniques are also useful for the exclusion of orbital fractures.

Other signs of blunt trauma should be sought. These include pupillary sphincter tears, iridodialysis, angle recession, cyclodialysis, trabecular dialysis, lens subluxation or dislocation, retinal dialysis and/or detachment, macular edema (commotio retinae), and choroidal rupture.[22] Gonioscopy (to detect angle recession, cyclodialysis, or trabecular dialysis) should not be performed until 4 weeks after the traumatic incident, as the attendant pressure on the globe may reopen an occult rupture of the globe, or promote rebleeding by

dislodging a blood clot from the injured vessel. Likewise, scleral indentation to detect peripheral retinal pathology should be deferred. If the hyphema is total, ultrasound examination may be useful to detect coincidental posterior segment pathology, such as vitreous hemorrhage, retinal detachment, and posterior lens dislocation. Where available, high-frequency ultrasound (ultrasound biomicroscopy) may detect anterior segment conditions masked by a total hyphema, such as lens subluxation or angle recession.[23]

With the slit lamp, a search is made for corneal blood staining. Pathologic studies of blood staining demonstrate erythrocyte breakdown products and hemosiderin in the keratocytes and corneal stroma.[24] Initially, this will manifest as a subtle yellowish discoloration of the posterior corneal stroma. Although corneal blood staining requires a high IOP, it may occur in the absence of glaucoma if there is corneal endothelial damage. When corneal blood staining is detected, this in itself may be an indication for surgical evacuation of the hyphema.

The visual acuity should be correlated with the amount of hyphema and coincidental ocular pathology. The presence of profoundly reduced vision (no light perception or bare light perception) that is not explained by the amount of hyphema or posterior segment problems should alert the examiner to the possibility of traumatic optic neuropathy, which may require megadose steroid therapy or surgical decompression of the optic canal.[25] Nevertheless, many patients with hyphema manifest afferent pupillary defects caused by the intraocular blood itself, rather than by the optic nerve injury.[13]

The IOP is measured by applanation tonometry or pneumatonometry. Ocular pressure by palpation is avoided in the acute period for reasons similar to gonioscopy and scleral indentation. Examination of the fellow eye is essential to provide a baseline IOP or to rule out the possibility of preexisting primary glaucoma in the injured eye.

If the patient is of African descent, a search should be made for sickle cell disease, including hemoglobin electrophoresis. If sickle cell disease is present, management will have to be more aggressive. Similarly, diabetes is also ruled out.

What Is the Differential Diagnosis of Hyphema with Glaucoma?

If the patient does not have a history of trauma, and there are no signs suggestive of trauma, other causes of hyphema should be considered, as any of them may be accompanied by glaucoma. These include neovascular glaucoma, herpetic iridocyclitis, retinoblastoma, uveal malignant melanoma, and juvenile xanthogranuloma.

Treatment and Management

How Is Glaucoma Complicating Hyphema Managed?

Management should be directed toward three main aims: encouraging resorption of hyphema, prevention of rebleeding, and treatment of elevated IOP.

To encourage hyphema resorption, activity should be restricted. For simple hyphema, outpatient management with limited activity and a shield may

suffice.[26,27] For severe cases and sickle cell patients, hospitalization with bed rest is mandatory.

Many drugs have been used to accelerate resorption of hyphema, including intravenous hyperosmotic agents (urea and mannitol), subconjunctival methylprednisolone,[28] systemic acetazolamide, topical atropine and pilocarpine,[29] and intracameral tissue plasminogen activator (TPA),[30] but none has been shown to have a clinically significant benefit. Although TPA was found in a rabbit model to accelerate hyphema resorption, it also substantially increased rebleeding episodes.[30]

Prevention of rebleeding is achieved by inhibition of clot lysis. Two antifibrinolytic agents, aminocaproic acid[31–33] and tranexamic acid,[34] have been tried, with equivocal results. Aminocaproic acid often causes nausea, vomiting, systemic hypotension, and dizziness, and has not been universally accepted. Furthermore, both drugs may precipitate thrombotic episodes in predisposed patients, such as patients with coronary artery disease. Because of these considerations, antifibrinolytics are reserved for patients at high risk of complications related to rebleeding, such as those with sickle cell disease, and perhaps all black patients.[13]

Elevated IOP associated with hyphema usually responds favorably to topical aqueous suppressant therapy, such as beta-blockers and α_2-agonists. CAIs may also be added when required. However, systemic acetazolamide is better avoided in sickle cell patients, as it increases ascorbate levels in the aqueous humor and produces systemic acidosis, both of which exacerbate erythrocyte sickling.[19] Methazolamide may be safer as it causes less systemic acidosis than acetazolamide.

When elevated IOP cannot be controlled medically and threatens to damage the optic nerve head, or if the hyphema is associated with corneal blood staining, surgical intervention is indicated. The critical level of IOP that warrants intervention depends on the status of the optic nerve head and the patient's general medical status. A healthy optic nerve may tolerate pressures of up to 40 or 50 mm Hg for a week or longer, whereas a glaucomatous disc may suffer further damage with substantially lower pressures within a shorter time period. Evaluation of the fellow eye may provide important information on preexisting glaucoma. Even the slightest IOP rise should be taken more seriously in sickle cell patients, as they are more prone to retinal artery occlusion.[13]

The optimal time for surgical intervention is controversial. Rebleeding is more frequent if intervention is instituted early. Furthermore, if intervention is delayed 3 to 5 days, many cases will resolve spontaneously. Four days has been suggested as the optimal time for surgical intervention with total hyphemas, as this allows optimal clot retraction without adherence to adjacent tissues.[35]

Various surgical approaches have been utilized successfully. The simplest of these is anterior chamber washout by irrigation through a paracentesis, with or without fibrinolytics.[36,37] Cases with more extensive clotting may require clot aspiration with the aid of ultrasonic emulsification or vitrectomy instrumentation. [38,39] In such cases, complete clot removal is neither safe nor necessary. Repeated attempts to disengage the clot may result in iris, lens, or angle damage, or invite rebleeding. Alternatively, the clot may be expressed out of the anterior chamber through a corneoscleral incision with the aid of a viscoelastic agent.[40,41] Trabeculectomy with gentle irrigation through a separate paracentesis

track may allow almost total removal of the clot, with at least temporary IOP control.[42] Although permanent filtration usually is not established, the trabeculectomy often affords subconjunctival filtration for a few weeks while trabecular meshwork function recovers.

Hemolytic Glaucoma

Definition

What Is Meant by Hemolytic Glaucoma?

Hemolytic glaucoma is an open-angle glaucoma that occurs within days to weeks after a large intraocular hemorrhage.

What Is the Mechanism of IOP Elevation in Hemolytic Glaucoma?

The mechanism of IOP elevation is an obstruction of the trabecular meshwork by macrophages laden with pigment, erythrocytes, and debris.[43,44] One ultrastructural study demonstrated that the condition is also associated with degenerative changes in trabecular endothelial cells that had phagocytosed blood.[45] Most commonly, the condition is self-limited but may persist, requiring management as discussed below.

Epidemiology and Importance

What Are the Risk Factors for Hemolytic Glaucoma?

The main risk factor for hemolytic glaucoma is intraocular hemorrhage, whether hyphema or vitreous hemorrhage.

Diagnosis and Differential Diagnosis

How Is Hemolytic Glaucoma Diagnosed?

The condition is diagnosed with the slit lamp by the presence of reddish-brown cells in the aqueous humor. There should be associated intraocular hemorrhage, in the form of hyphema and/or vitreous hemorrhage.

If the trauma is not recent, gonioscopy may be performed. Gonioscopy reveals an open angle without neovascularization. The trabecular meshwork may be covered with reddish-brown pigment, especially inferiorly.[44] The condition may also be confirmed by cytologic examination of the aqueous, which characteristically shows macrophages filled with golden brown pigment.[44]

What Is the Differential Diagnosis of Hemolytic Glaucoma?

Hemolytic glaucoma is associated with intraocular hemorrhage, which does not necessarily have to be traumatic in origin. Apart from trauma, other causes

of intraocular hemorrhage include proliferative diabetic retinopathy, hypertension, intraocular tumors, retinal detachment, sickle cell retinopathy, and retinopathy of prematurity. Hemolytic glaucoma may also be confused with ghost cell glaucoma, which is discussed below. Fortunately, the management of both hemolytic and ghost cell glaucoma is the same.

Treatment and Management

How Is Hemolytic Glaucoma Treated?

The condition usually responds to medical management with beta-blockers, α_2-agonists, CAIs, and hyperosmotic agents. Typically, the problem is self-limiting, and the drugs may be gradually tapered. Resistant cases may require surgical intervention, such as anterior chamber washout (with cytologic evaluation of the aqueous to confirm the diagnosis) or pars plana vitrectomy.[44]

Hemosiderotic Glaucoma

Definition

What Is Meant by Hemosiderotic Glaucoma?

This is a rare condition associated with a long-standing intraocular hemorrhage.

What Is the Mechanism Underlying Hemosiderotic Glaucoma?

The exact mechanism is unclear. It has been postulated that hemoglobin released from degenerated erythrocytes is phagocytosed by endothelial cells of the trabecular meshwork. The iron liberated by the hemoglobin causes siderosis of the trabecular meshwork, obstructing aqueous outflow.[46] It is thus a form of secondary open-angle glaucoma.

Epidemiology and Importance

What Are the Risk Factors for Hemosiderotic Glaucoma?

The main factor predisposing to this condition is the presence of a long-standing intraocular hemorrhage, allowing erythrocytes to degenerate and release their hemoglobin content.

Diagnosis and Differential Diagnosis

How Is the Condition Diagnosed?

In addition to the presence of a long-standing intraocular hemorrhage, whether hyphema or vitreous hemorrhage, gonioscopy should reveal an open angle with rusty brown discoloration.

What Is the Differential Diagnosis?

Hemosiderotic glaucoma should be distinguished from other open-angle glaucomas associated with intraocular hemorrhage. Hemolytic glaucoma is differentiated from hemosiderotic glaucoma by the presence in the former of reddish-brown blood cells, and reddish brown pigment covering the trabecular meshwork, especially inferiorly. Ghost cell glaucoma is characterized clinically by the presence of khaki-colored cells in the aqueous and vitreous, which may settle in the angle, especially inferiorly, or may be so numerous as to cause a pseudohypopyon.

As with all glaucomas associated with intraocular hemorrhage, the inciting hemorrhage may be of traumatic or nontraumatic origin.

Treatment and Management

How Is Hemosiderotic Glaucoma Managed?

The initial management of hemosiderotic glaucoma consists of lowering the IOP using beta-blockers, α_2-agonists, CAIs and, when necessary, hyperosmotic agents. If medical treatment fails to control the condition, it may be due to advanced siderotic angle damage, and filtering surgery may be appropriate. However, intraocular hemorrhage may require washout (hyphema) or vitrectomy (vitreous hemorrhage).

Ghost Cell Glaucoma

Definition

How Is Ghost Cell Glaucoma Defined?

Ghost cell glaucoma is an open-angle glaucoma associated with degenerated erythrocytes (ghost cells).

What Is the Mechanism of Ghost Cell Glaucoma?

After a prolonged vitreous hemorrhage, ghost cells develop in the vitreous and subsequently migrate to the anterior chamber through a disrupted anterior hyaloid face. As the erythrocytes degenerate in the vitreous, they change from their typical biconvex shape to spherical khaki-colored ghost cells (erythroclasts). The latter are more rigid than normal erythrocytes and less able to pass through the trabecular meshwork.[47] The condition is often transient, with the IOP returning to normal levels after the denatured cells clear from the anterior chamber angle. However, this may take months.

The onset of ghost cell glaucoma is typically 2 to 3 weeks following trauma, as it takes at least 1 to 2 weeks for erythrocytes to degenerate into ghost cells.[48,49] The degree of IOP elevation depends on the number of ghost cells reaching the anterior chamber. If the number of cells is small, the IOP may be normal, and if sufficient cells are present, the IOP may reach 50 or 60 mm Hg.

Epidemiology and Importance

What Are the Risk Factors for Ghost Cell Glaucoma?

The main risk factor is vitreous hemorrhage that persists long enough to allow erythrocyte degeneration. The second is disruption of the anterior hyaloid, which allows the degenerated cells to pass forward to the anterior chamber. Both of the above events may occur as a result of ocular trauma, or from non-traumatic causes, as discussed above.

A small hyphema is unlikely to produce ghost cell glaucoma. However, in the setting of an eight-ball or near-total hyphema, ghost cells may form, which may contribute to a prolonged IOP elevation seen even after removal of the blood. Aspirates from eight-ball hyphema show a significant number of ghost cells hidden within the clot.[50]

Diagnosis and Differential Diagnosis

How Is Ghost Cell Glaucoma Diagnosed?

As mentioned above, the degree of IOP elevation is variable. If the IOP is in the 50 to 60 mm Hg range, there may be severe ocular pain.

With the slit lamp, using high magnification and a narrow slit beam, ghost cells are seen in the anterior chamber as tiny khaki-colored cells. If the cornea is edematous from marked pressure elevation, a drop of topical glycerol may be needed to clear the cornea and permit a clearer view of the aqueous. Occasionally, these cells may collect inferiorly in the anterior chamber, forming a khaki-colored layer. If fresher erythrocytes have also reached the anterior chamber, they too may form a layer.[51]

Gonioscopy may be normal. If there are enough ghost cells, they may deposit on the trabecular meshwork, giving it a khaki hue, especially in the inferior angle. The lens may be subluxated or dislocated. Ophthalmoscopy usually will reveal vitreous hemorrhage. If the lens is cataractous, ultrasonography may be needed to confirm the presence of vitreous hemorrhage.

In doubtful cases, an aqueous sample may be obtained for cytologic diagnosis. After topical anesthesia, a 30-gauge needle is used to aspirate aqueous through a temporal paracentesis.[52] The aqueous sample is then spread on a slide and examined by phase contrast microscopy.[53,54] Ghost cells appear as spherical cells with a thin membrane. Clumps of degenerated hemoglobin (Heinz bodies) are seen adhering to the internal aspect of the cell membrane. Unlike hemolytic glaucoma, there are few, if any macrophages. Methyl violet 1% staining may aid in the diagnosis,[55] and the aspirate can be subjected to scanning and transmission electron microscopy, where available.[54]

What Is the Differential Diagnosis of Ghost Cell Glaucoma?

Ghost cell glaucoma does not necessarily have to occur in the setting of trauma. Originally, ghost cell glaucoma was described following pars plana vitrectomy.[56]

This is particularly liable to occur if only core vitrectomy is performed, leaving a large peripheral skirt of vitreous containing hemorrhagic debris. Because pars plana vitrectomy often disrupts the anterior hyaloid, it provides a route for ghost cells to reach the vitreous.

Ghost cell glaucoma can also occur after cataract extraction if the anterior hyaloid is disrupted. Two scenarios are possible. The first possibility is that the vitreous hemorrhage existed preoperatively. In such a case, ghost cells are released from an existing reservoir, and pressure elevation may occur only a few days after surgery. In the second scenario, the surgery is complicated by hyphema, and the erythrocytes pass backward into the vitreous cavity through a disrupted anterior hyaloid face. The hyphema may produce a transient IOP rise in the early postoperative period, and then weeks later the IOP may rise again as a result of ghost cells reaching the anterior chamber.[57] It is worth noting that the presence of an intraocular lens does not preclude the occurrence of ghost cell glaucoma.[58]

It is also possible that ghost cell glaucoma occurs without prior surgery or trauma, for example in long-standing diabetic vitreous hemorrhage when a defect in the anterior hyaloid develops, presumably spontaneously, as the vitreous liquefies.[59]

Similar to ghost cell glaucoma, neovascular glaucoma can also cause a sudden and high IOP elevation, together with corneal edema. There may also be an associated vitreous hemorrhage. To differentiate the two conditions, a drop of glycerol is used to clear the cornea. In neovascular glaucoma, rubeosis may be seen at the pupillary margin or the angle, together with synechial angle closure, neither of which is seen in ghost cell glaucoma. In neovascular glaucoma, there are no ghost cells in the anterior chamber.[51]

The combination of cells in the anterior chamber with elevated IOP is also seen in hemolytic glaucoma and glaucoma complicating uveitis. In hemolytic glaucoma, the cells are reddish-brown rather than khaki brown. In glaucoma complicating uveitis, the cells are leukocytes, not khaki-colored ghost cells. Typical signs of uveitis are circumcorneal ciliary injection, keratic precipitates, and anterior and posterior synechiae. In ghost cell glaucoma, the conjunctiva is usually white and quiet despite the presence of corneal edema, the ghost cells show no tendency to adhere to the cornea, and there are no synechiae. Questionable cases may require anterior chamber aspiration for resolution of the diagnosis.[51] Figure 13–4 summarizes the differential diagnosis of posttraumatic IOP elevation associated with cells in the anterior chamber.

Treatment and Management

How Is Ghost Cell Glaucoma Managed?

Initial management consists of medically lowering the IOP by aqueous suppressants such as beta-blockers, α_2-agonists, and CAIs. Miotics are of doubtful value.

If the pressure does not respond to medical management, anterior chamber washout is performed using a blunt cannula inserted into the anterior chamber through a temporal paracentesis. Balanced salt solution is injected into the

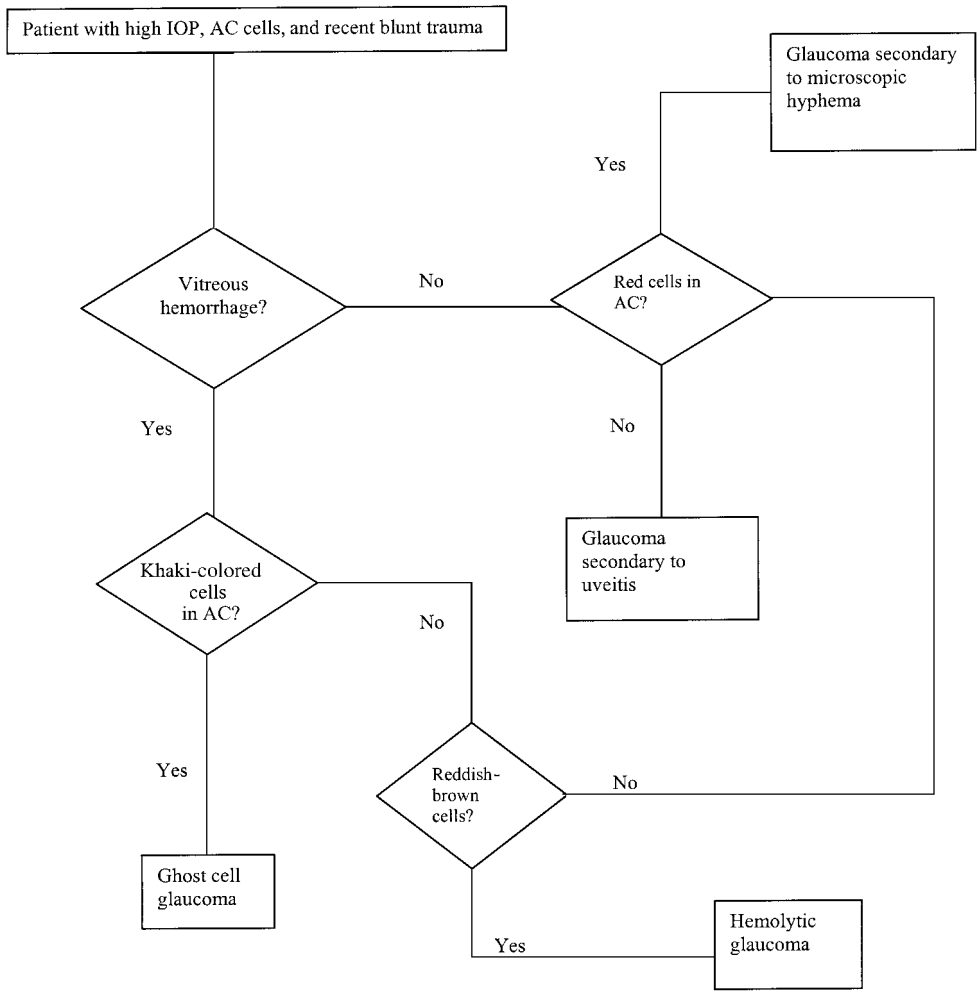

Figure 13–4. High IOP and anterior chamber cells after recent blunt trauma.

angle, and the paracentesis should be wide enough to allow egress of fluid. Approximately 10 mL of fluid are usually needed to wash out the ghost cells from the angle. Before the procedure, an aqueous sample may be obtained for cytologic examination.[51]

If the IOP remains elevated despite repeated anterior chamber washouts, this indicates that there is still a reservoir of ghost cells in the vitreous. In such a case, pars plana vitrectomy is required to resolve the condition.[58,60,61] Special attention must be given to the removal of all ghost cells, including those in the vitreous base. If the offending ghost cells are not completely removed, the remaining cells are released by the vitrectomy procedure, actually worsening the condition.[61]

Angle Recession Glaucoma

Definition

How Is Angle Recession Glaucoma Defined?

This is a chronic open-angle glaucoma that occurs secondary to posttraumatic angle recession.

What Is the Mechanism of IOP Elevation in Angle Recession Glaucoma?

Angle recession is a deepening of the anterior chamber angle resulting from a tear in the face of the ciliary body between the scleral spur and the iris root, frequently occurring between the circular and longitudinal muscles of the ciliary body. In most cases, at least 180 degrees of the angle needs to be affected for IOP elevation to develop. Characteristically, the IOP elevation occurs years after the initial trauma that caused angle recession. In a series of 18 patients with angle recession, Herschler[62] reported that the mean duration between initial trauma and the discovery of IOP elevation was 16 years.[62] Mermoud et al[63] studied 65 patients with angle recession and found that the latency period between injury and diagnosis of glaucoma averaged 7.6 ± 9.5 years.

The exact mechanism of IOP elevation in association with angle recession is controversial. It has been suggested that angle recession provides evidence of past injury but is not the actual cause of the glaucoma. It is believed, rather, that the initial trauma causes degeneration or proliferative changes in the trabecular tissue, which decrease outflow facility.[64] Another theory is that the cause of glaucoma is the formation of a Descemet-like membrane that grows from the cornea over the anterior chamber angle.[64–66]

Epidemiology and Importance

What Is the Incidence of Angle Recession Following Blunt Trauma?

The incidence of angle recession following blunt trauma varies in different reports from 60 to 94%.[2,15,67–69] Therefore, it should be suspected in every case of blunt ocular trauma, regardless of IOP level. Bilateral angle recession has been reported in 55 to 59% of South African patients with angle recession.[63,70]

What Are the Risk Factors For IOP Elevation Following Angle Recession?

The risk of IOP elevation after angle recession appears to be correlated with the extent of angle recession. Studies have shown that all patients who developed IOP elevation had greater than 180 degrees of angle recession.[67,71] Similarly, Salmon et al[70] reported that the prevalence of glaucoma in 146 eyes with angle recession of any degree was 5%, whereas in eyes with 360-degree angle recessions, the prevalence of glaucoma was 8%.

Spaeth[72] has reported that "normal" fellow eyes in patients with unilateral angle recession glaucoma are more likely to have elevated IOP and a positive response to corticosteroid-provocative testing. It has been suggested, therefore, that eyes with an underlying tendency to develop open-angle glaucoma are more likely to develop a late increase in IOP after blunt trauma.[62,72]

Diagnosis and Differential Diagnosis

How Is Angle Recession Glaucoma Diagnosed?

The classic presentation of angle recession glaucoma is a unilateral IOP elevation with optic disc excavation and visual field loss.[73] Angle recession is suspected when the anterior chamber appears abnormally deep. The typical gonioscopic appearance of angle recession consists of a widened ciliary body band with prominence of the scleral spur. This may be present in the whole angle, or only in scattered areas. However, this appearance may change as the tear in the ciliary body begins to scar, leading to the formation of peripheral anterior synechiae with obliteration of the angle recess. Thus, the initial depth and extent of angle recession may diminish with time. In such cases, other signs of blunt trauma may provide a valuable clue for diagnosis. Such signs include tears of the trabecular meshwork, iridodialysis, cyclodialysis, pupillary sphincter tears, absent or torn iris processes, iridoschisis, iridodonesis, phacodonesis, Vossius ring (an imprint of the pupil on the anterior caspule following blunt trauma), and dark brown to black deposits (small residua of hyphema) in the angle recess inferiorly.[13]

As mentioned above, angle recession may be bilateral. Therefore, gonioscopy of the fellow eye is mandatory, and is very helpful for comparison purposes. When angle recession is found, the IOP does not necessarily have to be elevated. There may be coincidental pathology decreasing the IOP (e.g., cyclodialysis), effectively "neutralizing" the IOP-elevating effect of angle recession. The other possibility is that the causative injury was relatively recent, and that the pressure elevation has not yet set in. There is usually a latent period of several years following trauma before glaucoma manifests itself. Finally, not every case of angle recession will be associated with IOP elevation.

What Is the Differential Diagnosis of Angle Recession Glaucoma?

The IOP elevation associated with angle recession is insidious in onset, asymptomatic, and typically unilateral. Therefore, the differential diagnosis of angle recession glaucoma includes all causes of chronic unilateral glaucoma, such as glaucoma associated with the pseudoexfoliation syndrome, uveitic glaucoma, glaucoma complicating intraocular tumors, neovascular glaucoma, and other causes of traumatic glaucoma. Furthermore, the condition may be superimposed on primary open-angle glaucoma, in which case examination of the fellow eye may reveal IOP elevation, an open angle, optic disc changes, and visual field loss.

Treatment and Management

How Is Angle Recession Glaucoma Managed?

Angle recession is fairly resistant to treatment. Initially, aqueous suppressants are tried, namely beta-blockers, α_2-agonists, and CAIs. Pilocarpine was reported to cause a paradoxical increase in IOP in one eye.[74] It is probable that the primary mechanism of aqueous drainage in that eye was uveoscleral outflow, because of damage to the trabecular meshwork. Pilocarpine is known to inhibit uveoscleral outflow in humans.

If medical treatment fails, some form of surgery is required. The average success rate of argon laser trabeculoplasty (ALT) in angle recession glaucoma is approximately 25%.[75,76] Argon laser trabeculopuncture is an alternative to ALT that has a variable success rate in the literature, ranging from 42% [77] to 91%.[76]

Filtering procedures are less frequently successful in angle recession glaucoma than in primary open-angle glaucoma (POAG). Mermoud et al[78] reported that the success rate of filtering surgery in angle recession glaucoma was 52% versus 89% for POAG at 1 year after surgery, 32% versus 84% at 2 years, and 8% versus 76% at 3 years. The main reason for failure was fibrosis of the fistula or filtering bleb.[78]

Given the relatively poor success rate of filtering surgery and the propensity to fibrosis, it is probably worthwhile in these eyes to perform primary filtering surgery with antimetabolites such as 5-fluorouracil (5-FU) or mitomycin C (MMC). In another study, Mermoud et al[63] compared trabeculectomy alone to trabeculectomy with MMC or 5-FU, and demonstrated a significantly higher success rate with MMC at 1 and 2 years after surgery.[63] Finally, if filtering surgery with antimetabolites fails, a seton procedure is required.

Glaucoma Secondary to Trabecular Injury

Definition

What Is Meant by Glaucoma Secondary to Trabecular Injury?

This is an IOP elevation that occurs secondary to trabecular injury, without the presence of angle recession.

What Is the Mechanism of Glaucoma Secondary to Trabecular Injury?

Trabecular meshwork injury occurs in the form of edema or tears. Tears of the trabecular meshwork heal in their original position, and may be impossible to detect later. The tear itself does not decrease outflow facility, but the associated scarring of the trabecular meshwork may decrease outflow facility and cause secondary open-angle glaucoma. In addition, the untorn surrounding trabecular meshwork may sustain some reversible damage, which transiently contributes to the IOP rise.[13]

Typically, glaucoma secondary to trabecular injury occurs in the first few days after trauma. Depending on the extent and reversibility of trabecular damage, and the preexisting facility of outflow, the glaucoma may be transient, or it may persist and require definitive management.

Epidemiology and Importance

What Is the Incidence of Trabecular Injury Following Nonpenetrating Trauma?

The occurrence of trabecular injury following nonpenetrating trauma is often overlooked. When specifically sought, the incidence may be as high as 76%, particularly in injuries that are severe enough to cause hyphema.[62] As a result, trabecular injury is one of the commonest causes of early IOP elevation following trauma.

Diagnosis and Differential Diagnosis

What Are the Clinical Features of Glaucoma Complicating Trabecular Injury?

Trabecular injury should be suspected whenever there is early glaucoma following nonpenetrating trauma. The gonioscopic finding may be trabecular edema, or a tear in the trabecular meshwork. Early after trauma, these findings may be masked by concomitant hyphema or uveitis, although a mild hyphema may allow sufficient visualization of the angle to make the diagnosis. Later on, the gonioscopic findings become much more subtle, and the angle may even appear normal. If there is sufficient recovery of the trabecular meshwork, the glaucoma may resolve. Extensive trabecular damage may result in persistent glaucoma.

What Is the Differential Diagnosis of Glaucoma Complicating Trabecular Injury?

An early IOP rise following trauma can be due to trabecular injury, hyphema, or traumatic uveitis. Hyphema is distinguished by the finding of red blood cells in the anterior chamber, whereas uveitis is characterized by leukocytes in the anterior chamber. However, it is probably common for all three entities to coexist in different combinations, each contributing to IOP elevation.

After the acute phase has subsided, a persistent IOP rise due to trabecular injury should be differentiated from other secondary open-angle glaucomas occurring after trauma. These include entities associated with intraocular hemorrhage, such as hemolytic glaucoma, ghost cell glaucoma, and hemosiderotic glaucoma. Hemolytic glaucoma and ghost cell glaucoma both exhibit cells in the anterior chamber, which are absent in glaucoma resulting solely from trabecular injury. Hemosiderotic glaucoma, especially late, is not associated with cells in the anterior chamber, similar to glaucoma resulting from trabecular injury. However, hemosiderotic glaucoma may show a characteristic rusty brown discoloration, whereas trabecular injury may leave a normal-appearing angle. Siderotic glaucoma complicating an old ferrous iron body is another type of late-onset open-angle glaucoma complicating penetrating trauma. In such a case, there will be other signs of siderosis oculi, as discussed

later in this chapter. Angle-recession glaucoma may be confused with glaucoma complicating trabecular injury. In most cases, gonioscopy will resolve the problem. Again, both angle recession and trabecular injury may coexist in the same patient.

Finally, a late-onset glaucoma associated with ocular trauma and a normal-appearing angle may be simply primary open-angle that had been previously undiagnosed, or was accelerated by mild trabecular injury.

Treatment and Management

How Is Glaucoma Due to Trabecular Injury Treated?

Initially, IOP is lowered by aqueous suppressants as described above. If this succeeds, the patient is kept on medical treatment, and periodic attempts are made to taper therapy. If trabecular function recovers, treatment may be discontinued, or at least reduced. If the IOP fails to respond to medical therapy, filtering surgery is warranted.

Glaucoma Secondary to Traumatic Cataract

Definition

What Is Meant by Glaucoma Secondary to Traumatic Cataract?

This is an IOP elevation occurring in a patient having traumatic cataract resulting from nonpenetrating trauma.

What Is the Mechanism of IOP Elevation from Traumatic Cataract?

In some cases, the IOP elevation presumably results from lens swelling that produces relative pupillary block, which leads to angle closure. This may lead to glaucoma relatively early following the trauma. In other cases, the patient may present with an old traumatic cataract and pressure elevation due to associated angle recession.

Epidemiology and Importance

Is Traumatic Cataract a Risk Factor for Traumatic Glaucoma?

Patients who develop cataract as a result of nonpenetrating injury are more prone to glaucoma than patients who do not develop cataract. Coles[17] reported that in a series of patients with traumatic hyphema, glaucoma occurred in 42%

of patients with traumatic cataract versus only 15% of patients who did not have traumatic cataract.[17]

Traumatic cataract is also associated with a high risk of angle recession, as the trauma that is severe enough to cause cataract usually causes concomitant angle recession. In a series of 46 eyes with traumatic cataract in which gonioscopy was possible, Canavan and Archer[2] found a 96% incidence of angle recession.

Diagnosis and Differential Diagnosis

How Is Glaucoma Secondary to Traumatic Cataract Diagnosed?

Glaucoma due to pupillary block occurs relatively early after trauma. Examination will reveal a shallow anterior chamber together with cataractous changes in the lens. Gonioscopy may show anterior bowing of the iris (iris bombé) with iridocorneal apposition obscuring a variable portion of normal angle structures.

If the pressure rise is due to concomitant angle recession, it typically occurs years after the trauma (as previously discussed). The patient's main complaint may be visual due to the cataract, as the glaucoma associated with angle recession is asymptomatic. On examination, the lens is cataractous, and the anterior chamber is deep. Gonioscopy may show the typical changes of angle recession (see Angle Recession Glaucoma, above).

What Is the Differential Diagnosis of Glaucoma Complicating Traumatic Cataract?

Glaucoma due to pupillary block should be differentiated from other causes of traumatic glaucoma associated with a shallow anterior chamber and angle closure (Fig. 13–5). These include traumatic uveitis with ring synechiae, lens subluxation with incarceration of the lens in the pupil, forward rotation of the ciliary body with forward displacement of the iris-lens diaphragm, and malignant glaucoma.[13] Traumatic uveitis is usually associated with white blood cells and flare. Iris bombé is observed when posterior synechiae develop over 360 degrees around the pupil. The anterior chamber is relatively deep centrally, as opposed to the other conditions where the anterior chamber is shallow centrally, and the iris appears to be draped over the lens. Lens subluxation may be associated with phakodonesis. Forward rotation of the ciliary body is suspected when there is choroidal effusion, which may be seen ophthalmoscopically if the media are clear, or diagnosed by B-scan ultrasonography. Definitive diagnosis of ciliary body rotation is now possible with high-frequency ultrasound biomicroscopy.[79] Malignant glaucoma (aqueous misdirection syndrome) may also be differentiated from ciliary body rotation by ultrasound biomicroscopy.[79,80] The differential diagnosis of angle recession glaucoma is discussed above.

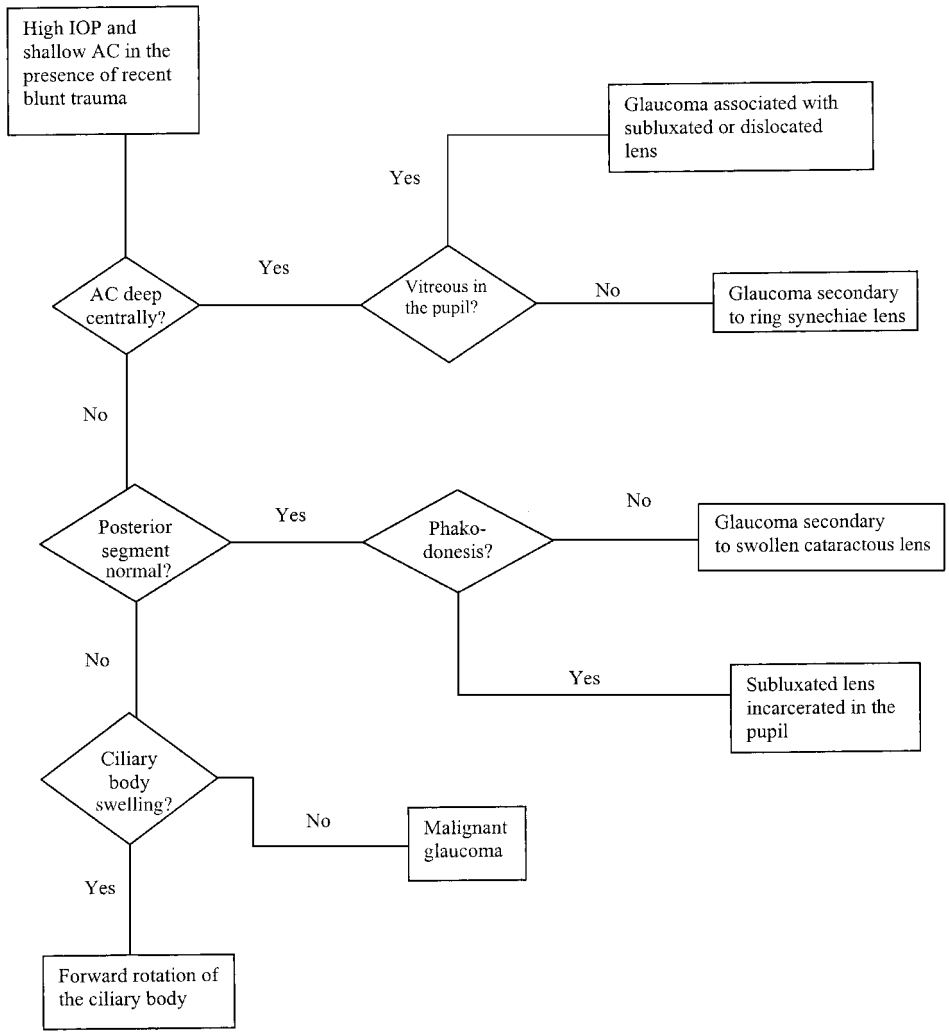

Figure 13–5. High IOP and a shallow anterior chamber after recent blunt trauma.

Treatment and Management

How Is Glaucoma Secondary to Traumatic Cataract Treated?

If a pupillary block mechanism is evident, neodymium:yttrium-aluminum-garnet (Nd:YAG) laser iridotomy is indicated to relieve pupillary block. If the cataract is visually significant, it may be removed at a later date. If the lens is severely cataractous, or if there is evidence of phakolytic glaucoma, cataract extraction may improve vision and restore normal IOP. The management of angle recession glaucoma is discussed above.

Glaucoma Secondary to Lens Dislocation

Definition

What Is Meant by Glaucoma Secondary to Lens Dislocation?

This is glaucoma caused by traumatic lens displacement as a result of nonpenetrating trauma. Lens displacement is caused by zonular disruption. Partial zonular disruption leads to subluxation of the lens, where the lens is displaced but remains partially or completely within the pupillary area. Total zonular disruption leads to lens dislocation, where the lens comes to lie completely in the anterior chamber (anterior dislocation), or falls back into the vitreous cavity (posterior dislocation).

What are the Mechanisms of Glaucoma Secondary to Lens Dislocation?

With lens subluxation, forward displacement of the lens or herniation of vitreous through the ruptured zonules may cause pupillary block and angle-closure glaucoma. With total anterior dislocation, angle-closure glaucoma may occur due to pupillary block, and open-angle glaucoma may occur from direct obstruction of the iridocorneal angle by the lens or lens fragments. Posterior lens dislocation is less likely to cause glaucoma than anterior dislocation. In such cases, glaucoma may occur due to herniation of vitreous through the pupil with pupillary block. If a posteriorly dislocated lens develops hypermature cataract, phakolytic glaucoma may occur.

Epidemiology and Importance

What Is the Incidence of Lens Dislocation Following Nonpenetrating Trauma?

Lens dislocation, whether subluxation or complete dislocation, is a very common sequela of nonpenetrating ocular injury and should be suspected in every case. Mieler et al[81] found that out of four golf-related nonpenetrating eye injuries, three were associated with lens dislocation. Chorich et al[82] also reported four eye injuries caused by bungee cords, in which two were associated with lens subluxation.

What Is the Incidence of Glaucoma Following Lens Dislocation?

Lens dislocation is a significant risk factor for traumatic glaucoma. In a retrospective review of 73 cases of glaucoma following nonpenetrating trauma, Sihota et al[83] found that 38.4% had some form of lens displacement. Rodman[84] reported a 77.5% incidence of glaucoma with anterior lens dislocation and 87.5% with subluxated or posteriorly dislocated lenses in a histopathologic review of 120 cases.

Diagnosis and Differential Diagnosis

How Is Glaucoma Secondary to Lens Dislocation Diagnosed?

As mentioned earlier, lens subluxation will lead to glaucoma if there is forward displacement of the lens with pupillary block, or if there is associated vitreous herniating through the pupil and causing pupillary block. In the first instance, there is a shallow anterior chamber, the iris appearing to be draped over the lens. The lens may show phakodonesis. If this is difficult to elicit, the subluxation may be suspected when there is myopic astigmatism that is not explained by keratometry, indicating that the astigmatism is lenticular in origin. In the second instance, there is more evident subluxation, with the edge of the lens being seen in the pupil. This is associated with vitreous prolapsing through the pupil, and a shallow anterior chamber. In both cases, gonioscopy will reveal iridocorneal apposition hiding the normal angle structures from view.

Anterior lens dislocation is diagnosed when the whole lens is found to be completely in front of the iris, often with lenticulocorneal touch. Posterior dislocation is diagnosed when there is aphakia without a history of cataract extraction. The lens is seen ophthalmoscopically in the vitreous cavity if the media are clear. If the glaucoma is due to pupillary block by vitreous, there will be a shallow anterior chamber with vitreous herniating through the pupil, and gonioscopic evidence of angle closure. If the glaucoma is phakolytic, there will be cells in the anterior chamber (macrophages filled with lens debris), and the dislocated lens appears hypermature.

Both subluxation and dislocation may be masked by concomitant corneal edema or intraocular hemorrhage. In such cases, the abnormal lens position may be confirmed by ultrasonography.

What Is the Differential Diagnosis of Glaucoma Secondary to Lens Dislocation?

Glaucoma due to incarceration of a subluxated lens in the pupil should be differentiated from other causes of traumatic glaucoma associated with a shallow anterior chamber. These include glaucoma secondary to traumatic cataract (without dislocation), traumatic uveitis with pupillary block, ciliary body rotation with forward displacement of the iris-lens diaphragm, and malignant glaucoma. This has been discussed above (see Glaucoma Secondary to Traumatic Cataract). Phakolytic glaucoma with a posteriorly dislocated hypermature lens is to be differentiated from other causes of traumatic glaucoma associated with cells in the anterior chamber, namely glaucoma secondary to hyphema, hemolytic glaucoma, ghost cell glaucoma, and glaucoma complicating traumatic uveitis. The differential diagnosis of these conditions has been discussed above (see Ghost Cell Glaucoma).

Treatment and Management

How Is Glaucoma Secondary to Lens Dislocation Treated?

Glaucoma secondary to anterior lens dislocation is usually associated with lens-corneal endothelial touch. Urgent lens extraction is indicated both to

relieve pupillary block and to prevent corneal endothelial decompensation. If the lens is soft, it may be removed by vitrectomy instrumentation. If the lens is hard, intracapsular extraction is more appropriate. In both cases, the procedure should include an anterior vitrectomy.

Pupillary block by vitreous may be relieved by Nd:YAG laser iridotomy. If lens extraction is indicated, anterior vitrectomy is performed at the time of lens extraction. A posteriorly dislocated lens usually does not cause problems. If the lens is hypermature and inducing phakolytic glaucoma, the lens is removed by pars plana vitrectomy techniques.

Glaucoma Secondary to Forward Displacement of the Iris-Lens Diaphragm

Definition

What Is Meant by Glaucoma Secondary to Forward Displacement of the Iris-Lens Diaphragm?

This a form of traumatic angle-closure glaucoma secondary to forward movement of the iris-lens diaphragm.

What Is the Cause of Forward Displacement of the Iris-Lens Diaphragm Following Nonpenetrating Trauma?

This may result either from forward rotation of the ciliary body due to posttraumatic choroidal or ciliary body edema,[85] or from malignant glaucoma (aqueous misdirection syndrome).[86]

Epidemiology and Importance

What Is the Risk of Glaucoma After Forward Displacement of the Iris-Lens Diaphragm?

The incidence of forward displacement of the iris-lens diaphragm after blunt trauma is very low.[85] However, when it does occur, the risk of glaucoma is high.

Diagnosis and Differential Diagnosis

How Is Forward Displacement of the Iris-Lens Diaphragm Diagnosed?

The condition is diagnosed when there is elevated IOP together with a shallow anterior chamber (see Fig. 13–5). The iris appears draped over an anteriorly displaced lens, as opposed to other causes of pupillary block where the anterior chamber appears relatively deep centrally with anterior bowing of the peripheral iris. Gonioscopy reveals angle closure due to iridocorneal apposition.

Ciliary body rotation is distinguished from malignant glaucoma by the presence of choroidal and/or ciliary body effusion. Choroidal effusion may be seen

ophthalmoscopically if the media are clear. Peripheral annular choroidal effusion and ciliary body effusion are best detected by ultrasonography. The absence of uveal effusion is highly suggestive of malignant glaucoma.[13]

What Is the Differential Diagnosis of Glaucoma Secondary to Forward Displacement of the Iris-Lens Diaphragm?

This includes all causes of elevated IOP associated with a shallow anterior chamber, namely forward rotation of the ciliary body, malignant glaucoma, pupillary block due to traumatic cataract (with lens swelling), pupillary block due to forward displacement of a subluxated lens, and pupillary block in association with traumatic uveitis. This has been discussed above (see Glaucoma Secondary to Traumatic Cataract).

Treatment and Management

How Is Glaucoma Secondary to Forward Displacement of the Iris-Lens Diaphragm Managed?

Forward rotation of the ciliary body is usually self-limited and is best treated by antiinflammatory agents such as corticosteroids and cycloplegics. Aqueous suppressants (beta-blockers, α_2-agonists, and CAIs) and hyperosmotic agents are used as necessary to control the IOP. Unless there is an associated pupillary block mechanism, iridotomy is neither necessary nor helpful.

Malignant glaucoma is treated initially with vigorous cycloplegia. If the condition fails to respond, posterior vitrectomy, often with lens extraction, is needed to relieve the aqueous misdirection.[13]

Glaucoma Secondary to Traumatic Uveitis

Definition

How Is Glaucoma Secondary to Traumatic Uveitis Defined?

This is an IOP elevation associated with uveitis secondary to nonpenetrating ocular trauma.

What Is the Mechanism of Glaucoma Secondary to Traumatic Uveitis?

There are several mechanisms by which traumatic uveitis can cause pressure elevation. The outflow pathways may become obstructed by inflammatory cells, debris, protein, or other serum components that are liberated because of vascular incompetence.[87] The trabecular endothelial cells may swell as a result of inflammation, compromising outflow. More severe inflammation may completely damage the trabecular endothelial cells. Chronic inflammation may

induce sclerosis of the trabecular meshwork. The trabecular meshwork may also become obstructed by a hyaline membrane. If posterior synechiae occur, this may lead to pupillary block and secondary angle closure.[88]

Epidemiology and Importance

How Often Is Uveitis Caused by Nonpenetrating Ocular Trauma?

Rosenbaum et al[89] studied a series of 496 patients with uveitis, and found 24 patients (4.8%) who had uveitis attributable to nonpenetrating trauma. In a series of 230 cases of anterior uveitis in children, Giles[90] reported that the incidence of traumatic uveitis was 1.3% (60% were idiopathic).

Diagnosis and Differential Diagnosis

How Is Glaucoma Secondary to Traumatic Uveitis Diagnosed?

Uveitis is diagnosed by the presence of flare and cells in the anterior chamber. There may also be posterior synechiae, with or without pupillary block and iris bombé. Gonioscopy may be normal or may show a hyaline membrane over the trabecular meshwork. If there is pupillary block, iridocorneal apposition may be seen on gonioscopy. Other effects of nonpenetrating trauma may be seen, such as lens subluxation, cataract, angle recession, and so on.

After the uveitis has resolved, the IOP may remain elevated as a result of permanent trabecular endothelial cell damage. Gonioscopy may be normal, so that the diagnosis can only be made by careful history taking, and the finding of other signs of nonpenetrating trauma.

What Is the Differential Diagnosis of Glaucoma Secondary to Traumatic Uveitis?

This includes other causes of traumatic glaucoma associated with cells in the anterior chamber. Inflammatory cells may be difficult to distinguish from red blood cells. Inflammation should be suspected if the IOP is elevated with a small number of cells in the anterior chamber, because a similar quantity of fresh erythrocytes would not be expected to induce ocular hypertension in eyes with normal facility of outflow. However, if IOP returns to normal after resolution of hyphema, only to rise later in association with fine tan-colored cells in the anterior chamber, ghost cell glaucoma rather than uveitic glaucoma should be suspected. Hemolytic glaucoma is associated with reddish brown cells in the anterior chamber, which represent macrophages engulfing hemolytic debris.

Glaucoma due to pupillary block should be differentiated from other causes of traumatic glaucoma associated with a shallow anterior chamber (see Diagnosis and Differential Diagnosis under Glaucoma Secondary to Forward Displacement of the Iris-Lens Diaphragm, above).

After resolution of inflammation, the presence of glaucoma due to postinflammatory trabecular damage may be confused with other causes of chronic secondary open-angle glaucoma following trauma. This includes angle-recession and siderotic glaucoma, both of which have characteristic gonioscopic findings (see above). Lastly, elevated pressure secondary to medical therapy for uveitis should also be considered, such as steroid-induced and mydriatic glaucoma.

Treatment and Management

How Is Glaucoma Secondary to Traumatic Uveitis Treated?

Initial treatment should consist of antiinflammatory and antiglaucomatous medications. Antiinflammatory medications include corticosteroids, nonsteroidal antiinflammatory drugs, and cycloplegics. Antiglaucomatous medications that may be used are aqueous suppressants such as beta-blockers, α_2-agonists, and CAIs. Miotics should be avoided as they increase blood–-aqueous barrier breakdown.

In cases with posterior synechiae and pupillary block, vigorous cycloplegia may break the synechiae and relieve the pupillary block. If this fails, prompt laser iridotomy is needed to reestablish normal aqueous flow.

In most cases, the IOP normalizes once inflammation resolves. If IOP elevation persists, and is uncontrollable by medication, filtering surgery may be indicated.

GLAUCOMA COMPLICATING PENETRATING TRAUMA

Definition

What Is Meant by Glaucoma Complicating Penetrating Trauma?

Penetrating (or "perforating") trauma is an injury to the globe that results in a full-thickness laceration of the ocular wall. This may or may not be associated with a retained intraocular foreign body. Occasionally, the injurious agent may pass through the anterior portion of the globe, traverse the eye, and exit again through the posterior part of the ocular wall, producing a double penetrating injury. A penetrating injury may produce elevation of the IOP, either acutely or as a delayed effect.

What Are the Mechanisms of Glaucoma Complicating Penetrating Trauma?

Several mechanisms may produce glaucoma in an eye that has sustained penetrating trauma. A prolonged flat anterior chamber may result in peripheral anterior synechiae. Intraocular inflammation is associated with glaucoma that results from a variety of mechanisms (see Glaucoma Secondary to Traumatic Uveitis, above). Inflammation of the uninjured fellow eye, known as sympathetic ophthalmia, may produce glaucoma in the uninjured eye. Intraocular

hemorrhage may occur following penetrating trauma, and may induce IOP elevation by several mechanisms, namely, glaucoma complicating hyphema, ghost cell glaucoma, hemolytic glaucoma, and hemosiderotic glaucoma. All forms of glaucoma associated with intraocular hemorrhage have been discussed above (see Glaucoma Complicating Nonpenetrating Trauma). Lens injury with violation of the lens capsule may also produce glaucoma, as will be discussed below. Epithelial down-growth and fibrous ingrowth may also cause glaucoma. A retained (and often missed) metallic foreign body may remain in the eye and cause chemical effects. Iron foreign bodies cause siderosis, and copper causes chalcosis, both conditions being associated with glaucoma.

Table 13–4 lists the causes of glaucoma complicating penetrating trauma.

What Are the Mechanisms of Lens-Induced Glaucoma in Association with Penetrating Trauma?

Lens injury may induce glaucoma through one of three mechanisms. The first is lens particle glaucoma glaucoma, where the trabecular meshwork becomes obstructed with cortical material and and inflammatory cells. Another mechanism is phacoanaphylaxis, where patients becomes sensitized to their own lens proteins and develop a granulomatous reaction around the lens. If the trabecular meshwork becomes involved in the inflammatory process, glaucoma may develop.[91] Alternatively, the lens may swell, causing relative pupillary block and secondary angle closure.[13]

What Is the Definition of Glaucoma Secondary to Epithelial Down-Growth and Fibrous Ingrowth?

A poorly apposed corneal or corneoscleral laceration may allow epithelial elements or fibrous tissue to invade the eye. Epithelial down-growth may manifest as an epithelial cyst in the anterior chamber, or a sheet-like growth. Fibrous ingrowth usually appears in the form a retrocorneal membrane. All these conditions may be associated with glaucoma, which is usually intractable.

What Is the Mechanism of Glaucoma Secondary to Epithelial Down-Growth and Fibrous Ingrowth?

An enlarging epithelial cyst may induce glaucoma by preventing aqueous from reaching portions of the angle. There may also be associated iritis, which may

Table 13–4. Types of Glaucoma Associated with Penetrating Trauma

Glaucoma secondary to flat anterior chamber
Glaucoma secondary to inflammation
Glaucoma secondary to intraocular hemorrhage
Lens-induced glaucoma
Glaucoma secondary to epithelial down-growth and fibrous ingrowth
Glaucoma secondary to siderosis
Glaucoma secondary to chalcosis

elevate the IOP by several mechanisms (see Glaucoma Secondary to Traumatic Uveitis, above).

Sheet-like epithelial down-growth produces glaucoma through several mechanisms. Hypotony, inflammation, and shallowing of the anterior chamber lead to broad peripheral anterior synechiae. Proliferating epithelium covers the trabecular meshwork, as well as the false angle caused by peripheral anterior synechiae. Areas of trabecular meshwork underlying the epithelial sheet undergo sclerosis and necrosis.[92] Chronic inflammation of the uvea leads to trabeculitis and decreased outflow facility. Pupillary block glaucoma is produced when the epithelial sheet occludes or secludes the pupil.[93] Hemorrhagic and ghost cell glaucoma may result from repeated hemorrhage from friable neovascularization. Chronic hypotony may progress to intractable glaucoma if the fistula closes, either spontaneously or iatrogenically.[94]

Glaucoma in association with fibrous ingrowth occurs from obliteration of the angle structures, and peripheral anterior synechiae occur from persistent flat anterior chamber or inflammation or recurrent bleeding from friable neovascularization, often leading to hemolytic glaucoma.[95,96]

What Is Meant by Glaucoma Secondary to Siderosis Bulbi?

Iron released from retained metallic foreign bodies is deposited in various intraocular structures resulting in toxic damage. This condition is termed siderosis bulbi. Involvement of the trabecular meshwork may lead to secondary open-angle glaucoma. Iron is also toxic to the retina.[13]

What Is Meant by Glaucoma Complicating Chalcosis?

Chalcosis is a condition where copper released from a retained intraocular foreign body is oxidized within the eye, producing tissue damage. Damage to the trabecular meshwork results in glaucoma.

Epidemiology and Importance

What Is the Incidence of Penetrating Ocular Trauma?

This varies according to sex and age, the incidence being higher at younger ages and in males. Thus, in 10- to 19-year-old males, the incidence of penetrating ocular trauma is 94.3 per million person-years, whereas in 60- to 69-year-old females, the incidence is 3.9 per million person-years.[1] Alcohol and illicit drug use increase the risk for penetrating ocular injury.[3]

What Are the Causes of Penetrating Ocular Trauma?

Penetrating injury may result from blunt forces (10–46%), sharp laceration (34–37%), or missiles (27–41%).[3,4,97,98] Intraocular foreign bodies were present in 6% of assault-related and 35% of occupational injuries in patients registered in the National Eye Trauma System (NETS).[3,4]

What Is the Incidence of Sympathetic Ophthalmia Following Traumatic Ocular Injuries?

The incidence of sympathetic ophthalmia following traumatic ocular injuries is 0.1 to 0.3%.[99–101] Jennings and Tessler[102] diagnosed sympathetic ophthalmia in 1.4% (20 patients) of the total number of referred patients with uveitis seen over an 11-year period.

How Long After Trauma Does Sympathetic Ophthalmia Occur?

Chan et al[103] studied 32 cases of sympathetic ophthalmia and found that 18 cases (56%) occurred within 1 year of injury. Eight patients (25%) developed the condition more than 3 years following injury. Two cases (6%) occurred within 2 weeks after injury; 10 cases (31%) between 2 weeks and 3 months; six cases (19%) between 3 months and 1 year; and four patients (13%) between 1 and 3 years. In one other patient, the interval between injury and the occurrence of the condition was 64 years.

What Are the Risk Factors for the Occurrence of Epithelial Down-Gowth and Fibrous Ingrowth After Penetrating Trauma?

The basic risk factor for both epithelial down-growth and fibrous ingrowth is poor wound closure, whether from faulty surgical technique or because of the nature of the wound (excessively lacerated with friable edges). Poor wound closure results in incarceration of tissue, serving as a wick that facilitates postoperative wound gape. Apposition of iris to the wound provides a source of nutrients for the proliferating cells. Chronic inflammation contributes to poor wound healing. Recurrent bleeding from a vascularized, inflamed wound is thought to provide a fibrin scaffold for fibrous proliferation into the anterior chamber.[94]

What Is the Incidence of Epithelial Down-Growth and Fibrous Ingrowth?

The incidence of these conditions is low, and decreasing over time, mainly due to advances in microsurgical techniques. Terry et al[104] estimated a rate of 0.35% epithelialization after traumatic and surgical perforations based on 28 diagnostic laboratory specimens out of 8,000 cases. Although most studies pertain to cataract surgery, they show the trend for epithelial down-growth to decrease over time; in the older literature, 17 to 26% of all enucleations after cataract surgery were due to this complication, whereas recently the incidence ranges from 0.12 to 0.08%.[105] Allen[106] reported an 11% incidence of fibrous ingrowth in 237 eyes enucleated for trauma. In general, the incidence of fibrous down-growth in enucleated eyes tends to be lower than epithelial down-growth.[107].

What Is the Incidence of Glaucoma Secondary to Siderosis and Chalcosis?

This is a relatively rare form of traumatic glaucoma. Percival[108] reported a series of 153 patients with posterior segment intraocular foreign bodies (iron or otherwise), in which only eight (5%) developed glaucoma that was not attributable to lens-induced mechanisms. Glaucoma appears to be less frequently associated with chalcosis than with siderosis.[109]

Diagnosis and Differential Diagnosis

How Is Glaucoma Secondary to a Flat Anterior Chamber Diagnosed?

In addition to elevated IOP, there are signs of a healed corneal or corneoscleral laceration. This laceration may have been sutured, or it may have been neglected, with the formation of anterior iris synechiae to the resultant scar. The anterior chamber may be irregular in depth. Gonioscopy will reveal a closed angle due to the presence of peripheral anterior synechiae.

What Is the Differential Diagnosis of Glaucoma Secondary to a Flat Anterior Chamber?

Other causes of a previously flat anterior chamber include corneal melting due to corneal infection (e.g., bacterial or herpetic), and sterile corneal melting as a result of collagen vascular disease (e.g., rheumatoid arhthritis). In such cases, there is no history of ocular trauma.

Peripheral anterior synechiae may form as a result of prolonged pupillary block associated with traumatic uveitis or a swollen cataractous lens, both of which may occur in the absence of penetrating trauma.

How Is Glaucoma Secondary to Inflammation Diagnosed?

Inflammation is a common sequela of penetrating trauma, and may induce pressure elevation. Inflammation may also occur in the fellow uninjured eye, presumably as a result of autosensitization of the eye to uveal pigment released into the systemic circulation at the time of trauma.[110,111] The condition is termed sympathetic ophthalmia, the injured eye being the "exciting" eye, and the fellow eye being the "sympathizing" eye. This may cause IOP elevation in *both* eyes.

As mentioned above, inflammation is diagnosed by the presence of flare and cells in the anterior chamber, with or without posterior synechiae. The latter may induce pupillary seclusion, which leads to iris bombé and secondary angle closure. Angle closure may be confirmed by gonioscopy.

Sympathetic ophthalmia presents as bilateral granulomatous uveitis. It is therefore mandatory to examine the fellow uninjured eye if uveitis is found in the injured eye. The first symptoms of sympathetic ophthalmia are photophobia and blurring of near vision due to loss of accommodation. In addition to the

usual signs of uveitis, there may be characteristic nodules occurring in the choroid, known as Dalen-Fuchs' nodules, representing foci of granulomatous inflammation.[112]

What Is the Differential Diagnosis of Glaucoma Complicating Inflammation?

Glaucoma complicating inflammation is to be differentiated from other types of traumatic glaucoma associated with cells in the anterior chamber. Pupillary block glaucoma is to be differentiated from other causes of traumatic glaucoma associated with a flat anterior chamber. This has been discussed above (see Glaucoma Secondary to Traumatic Uveitis). Examination of the fellow uninjured eye is essential to exclude sympathetic ophthalmia.

Sympathetic ophthalmia does not necessarily occur in the setting of unilateral accidental trauma. It may be induced by surgery in one eye, including cataract, glaucoma, and retinal detachment surgery, all of which may presumably result in uveal incarceration in the wall of the globe. Sympathetic ophthalmia should be differentiated from other causes of granulomatous panuveitis, such as the Vogt-Koyanagi-Harada syndrome.

How Is Lens-Induced Glaucoma Diagnosed?

Lens particle glaucoma glaucoma and glaucoma secondary to phakoanaphylactic uveitis are diagnosed by the presence of a corneal or corneoscleral laceration, violation of the lens capsule, and free lens matter and cells in the anterior chamber.

Relative pupillary block is diagnosed when there is a shallow anterior chamber with the iris appearing to be draped over a cataractous lens.

What Is the Differential Diagnosis of Lens-Induced Glaucoma?

Lens particle glaucoma and glaucoma secondary to phakoanaphylactic uveitis may be confused with other types of traumatic cataract associated with cells in the anterior chamber. This includes glaucoma complicating hyphema, hemolytic glaucoma, ghost cell glaucoma (all of which are associated with intraocular hemorrhage), and glaucoma complicating traumatic uveitis. In all these entities, the lens is intact, and there is no free lens matter in the anterior chamber.

Pupillary block due to a swollen cataractous lens may occur in association with nonpenetrating ocular trauma. In such a case, there is no evidence of corneoscleral lacerations, and there may be other signs of nonpenetrating trauma, such as pupillary sphincter tears and angle recession.

How Are Epithelial Down-Growth and Fibrous Ingrowth Diagnosed?

Epithelial down-growth may present as a cyst or sheet-like growth. The time interval between injury and the occurrence of epithelial down-growth is variable, ranging from a few days to 10 years.[94]

An epithelial cyst may be either translucent or gray in color, usually appearing connected at one point with the traumatic wound. Rarely, the cyst will appear disconnected from the wound. Occasionally, a cyst will present in the posterior chamber, and grow into the anterior chamber through a peripheral iridectomy, or erode through the iris. The appearance and rate of growth of these cysts is variable, and they usually stabilize after a period of continued growth. There may be associated glaucoma, iridocyclitis, and pupillary distortion, and if large enough, the cyst may occlude the visual axis.[94]

Sheet-like epithelial down-growth is more irritating to the eye, so that the patient usually complains of tearing and dull-aching pain. Photophobia and blurred vision are less frequent complaints. There is usually ciliary injection, and often wound gape, an inadvertent filtering bleb, or a fistula demonstrable by Seidel testing. Band keratopathy is occasionally present.[113] The cornea may or may not demonstrate edema overlying a posterior corneal membrane demarcated by a gray line, best seen on retroillumination. The gray line represents the edge of the advancing epithelial sheet, and may be scalloped, with focal pearl-like areas of thickening. Aqueous flare and cells may be present and indicate iridocyclitis; flare may be disproportionate to ciliary flush or symptoms.[114]

The epithelial membrane grows rapidly over the iris, often obscuring iris details. In brown irides, the advancing edge of the membrane may appear as an indentation in the iris. The pupil may be distorted.

On gonioscopy the epithelium may be seen as a sheet obscuring details of the trabecular meshwork. Peripheral anterior synechiae are often present. Gonioscopy can be used to assess the extent of epithelialization of the angle, through an iridectomy, and sometimes over the ciliary body and retina.[94]

Fibrous ingrowth is most commonly recognized as a retrocorneal membrane. Usually, the condition does not make the eye uncomfortable. The membrane may resemble an epithelial sheet, appearing as a translucent membrane with a fairly distinct border. More commonly, the membrane appears gray and felt-like with a frayed leading margin. The overlying cornea is usually edematous. Extension of the membrane over the iris, angle, and vitreous is easily recognized as a thick enveloping membrane. The pupil may be drawn into the fibrous scar.

The condition may be fairly quiescent with minimal accompanying inflammation, or there may be massive fibrous intraocular proliferation, and later retraction, resulting in retinal detachment, hypotony, and phthisis bulbi.[94]

What Is the Differential Diagnosis of Epithelial Down-Growth and Fibrous Ingrowth?

Epithelial cysts should be differentiated from congenital cysts of the iris stroma, which may be pigmented, arising from the pigment epithelium, or nonpigmented, arising from the iris stroma.[115] Pigmented cysts are easy to differentiate from epithelial cysts, which are nonpigmented. On the other hand, congenital stromal cysts may be confused with epithelial cysts, but usually present at an earlier age, without a history of trauma or evidence of a penetrating wound.

Sheet-like epithelial down-growth is to be differentiated from other causes of retrocorneal membranes, such as a reduplicated Descemet's membrane (as

occurs in chronic iridocyclitis), detachment of Descemet's membrane, peripheral corneal edema (usually from operative endothelial trauma), and vitreocorneal adhesion, which may cause corneal edema and have a grayish appearance.[116] The posterior lip of a shelved corneal incision (as is commonly used for phacoemulsification) may also be confused with epithelial down-growth, but is nonprogressive as opposed to an epithelial sheet.[94]

Fibrous ingrowth has essentially the same differential diagnosis as sheet-like epithelial down-growth. Fibrous ingrowth is distinguished from epithelial down-growth by its slow growth and vascularity.

How Is Glaucoma Secondary to Siderosis Diagnosed?

The pressure elevation associated with siderosis bulbi is asymptomatic. If there is associated cataract, the vision may be affected, even in the absence of significant retinal damage. If the lens is clear, vision may be impaired by advanced retinal damage.

In addition to pressure elevation, there is a constellation of signs due to iron deposition in the various ocular tissues. Iron deposition in the iris produces heterochromia, and mydriasis results from toxic damage to the iris sphincter. The deep cornea and anterior subcapsular portion of the lens have a rust-brown color. Advanced retinal damage produces a retinitis pigmentosa-like picture. Gonioscopy reveals rust-brown discoloration of the angle. There may also be signs of previous perforation of the globe by the foreign body, such as a sealed corneal wound, a hole, or a transillumination defect in the iris. Occasionally, a foreign body may be directly visualized in the angle by gonioscopy, or in the posterior segment by ophthalmoscopy.[13]

To confirm the clinical suspicion of an intraocular foreign body, appropriate radiography, ultrasonography, and CT may be of help. Magnetic resonance imaging (MRI) should be avoided as the associated magnetic field may produce movement of the foreign body, which may result in intraocular damage.[117] Electrophysiologic testing may be used to assess retinal function; a depressed electroretinogram (ERG) indicates siderotic retinal damage.[118]

What Is the Differential Diagnosis of Glaucoma Complicating Siderosis Bulbi?

IOP elevation, a history of ocular trauma, rust-brown discoloration of the angle, and possibly mydriasis from traumatic iris sphincter rupture are also seen in hemosiderotic glaucoma (see above). However, the other signs of iron deposition seen in siderosis are absent. Angle recession glaucoma is another form of traumatic secondary open-angle glaucoma associated with traumatic mydriasis but is differentiated from siderotic glaucoma by its characteristic gonioscopic picture and the absence of other signs of siderosis.

How Is Glaucoma Secondary to Chalcosis Diagnosed?

There may be signs of foreign body entry such as a sealed corneal wound, a hole, or a transillumination defect in the iris. The foreign body may be seen in

the angle by gonioscopy, or in the posterior pole by ophthalmoscopy. Imaging studies may be needed to confirm the presence of a foreign body. The iridocorneal angle is open.

Copper may be deposited in the cornea, lens, vitreous, and retina. Copper deposits in the cornea appear as a golden brown, ruby red, or green pigment ring in the peripheral Descemet's membrane (Kayser-Fleischer ring). Lens opacities occur in the form of anterior subcapsular cataract.[112] Posterior segment examination may reveal fibrillary degeneration of the vitreous, and/or maculopathy secondary to copper deposition in the retina.[109] Vision may be affected by cataract, vitreous opacification, or maculopathy.

Electroretinographic (ERG) findings in chalcosis are not as striking as those seen in siderosis. If there is significant vitreous opacification, this may mildly depress the ERG; otherwise ERG is usually within the normal range.[109]

What Is the Differential Diagnosis of Chalcosis?

Chalcosis oculi is seen in Wilson's disease, primary biliary cirrhosis, chronic active hepatitis, exogenous copper administration, and progressive intrahepatic cholestasis of childhood. Wilson's disease is distinguished from other conditions by low serum ceruloplasmin and the presence of neurologic symptoms.[119] In all types of chalcosis not caused by an intraocular foreign body, the condition is characteristically bilateral. Unless there are bilateral foreign bodies, posttraumatic chalcosis is unilateral.

Figures 13–6 and 13–7 outline the differential diagnosis of IOP elevation following recent and old penetrating trauma.

Treatment and Management

How Is Glaucoma Secondary to a Flat Anterior Chamber Managed?

The best treatment for this problem is prevention, by meticulous initial closure of corneal and corneoscleral lacerations. In the early postoperative period, a flat or shallow anterior chamber, hyptony, and a positive Seidel test are indicators of wound leakage. A small leak may be initially managed with a bandage contact lens. If this fails to reform the anterior chamber, resuturing of the wound is indicated. If the wound edges are excessively friable, or if it is judged that adequate suturing would induce excessive astigmatism, cyanocrylate tissue adhesive is a useful tool.

If there is established glaucoma, initial management is by aqueous suppressants. Failure of medical treatment is an indication for filtering surgery.

How Is Glaucoma Secondary to Inflammation Treated?

Initial management consists of corticosteroids, cycloplegic agents, and aqueous suppressants. Laser iridotomy may be required for iris bombé. Persistent IOP elevation despite resolution of inflammation may be an indication for filtering surgery (see Glaucoma Secondary to Traumatic Uveitis, above).

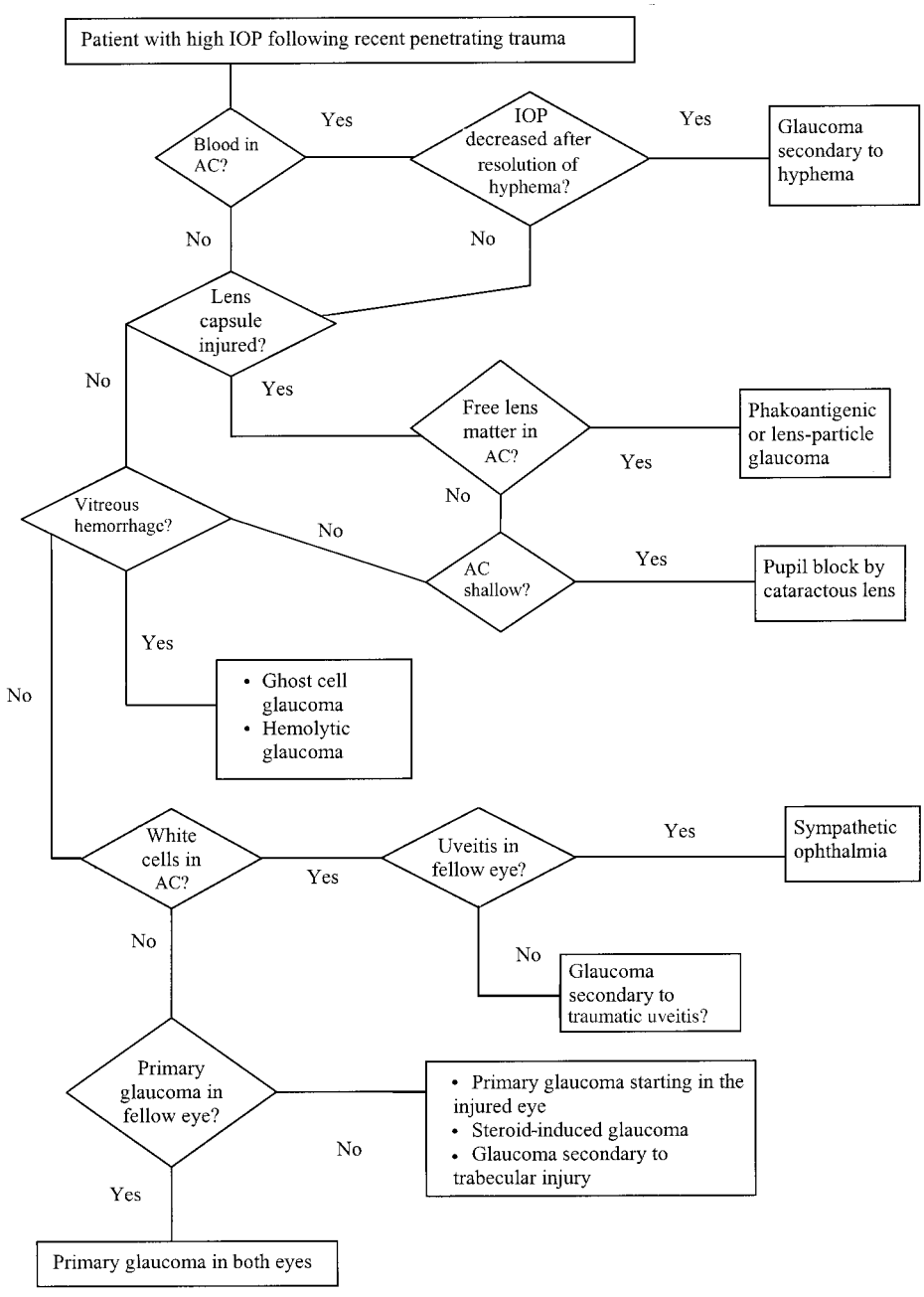

Figure 13–6. High IOP after recent penetrating trauma.

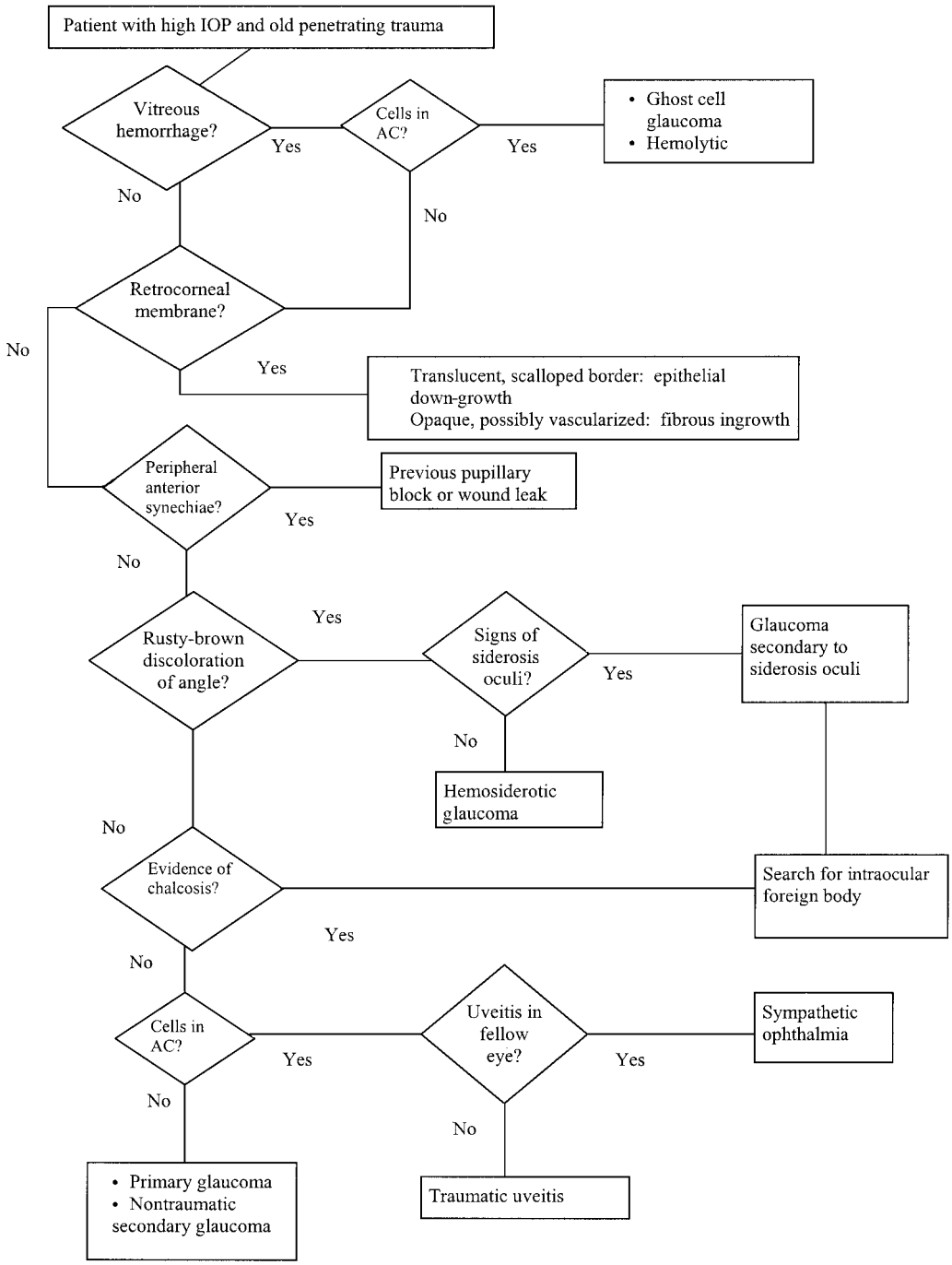

Figure 13–7. Differential diagnosis of high IOP with old penetrating trauma.

Sympathetic ophthalmia warrants special mention. The condition should always be suspected in the fellow eye in cases of penetrating ocular trauma. Once the condition is recognized, it should be treated aggressively with high doses of systemic corticosteroids and/or immunosuppressive drugs, usually for a prolonged period. The exciting eye should be removed if it does not have functional visual potential.[103]

How Is Glaucoma Secondary to Intraocular Hemorrhage (in Association with Penetrating Trauma) Treated?

Intraocular hemorrhage may complicate penetrating trauma and lead to several types of glaucoma, including glaucoma secondary to hyphema, hemolytic glaucoma, ghost cell glaucoma, and siderotic glaucoma. The management of these discussions is discussed above (see Glaucoma Complicating Nonpenetrating Trauma).

How Is Lens-Induced Glaucoma Treated?

Both lens particle glaucoma and glaucoma secondary to phakoanaphylactic uveitis are initially treated with aqueous suppressants to decrease IOP, corticosteroids to control inflammation, and mydriatics to prevent and/or treat posterior synechiae. If the IOP remains elevated, lens removal is indicated.[91].

Relative pupillary block due to a swollen lens is also treated by lens removal. Initially, pharmacologic mydriasis or a laser iridotomy may relieve the pupillary block. If this fails, aqueous suppressants are given until the lens is removed.[13]

How Is Glaucoma Complicating an Epithelial Cyst Managed?

An epithelial cyst that is causing glaucoma should be widely excised, if possible intact. Large cysts that are adherent to the cornea, iris, or vitreous face are first collapsed using a 25-gauge needle. If the collapsed cyst is small, it is frozen through the cornea after an insulating air bubble is placed in the anterior chamber. Larger cysts may require vitrectomy instruments to remove adherent vitreous and iris, whereas epithelial remnants are frozen as described above. If surgical excision and freezing result in persistent corneal edema, penetrating keratoplasty may be subsequently performed to improve vision.[120]

How Is Glaucoma Complicating Sheet-Like Epithelial Down-Growth Managed?

Management has two aims: removing epithelial tissue and controlling glaucoma. If there is a Seidel-positive fistula (where the epithelial cells have entered), this should be closed, if necessary with the use of patch grafts.[121] Preoperatively, the involved iris is marked with photocoagulation spots. The iris and vitreous with adherent epithelium are removed with vitrectomy instruments through the pars plana. Generous anterior vitrectomy is performed followed by air/fluid exchange. Epithelial tissue on the corneal endothelium, iridocorneal angle, ciliary body, and peripheral retina are treated with transcorneal and transscleral cryotherapy. If there is extensive involve-

ment of the cornea, penetrating keratoplasty may be needed. Despite significant advances in microsurgery, epithelial down-growth remains a highly challenging problem with a high rate of recurrence.[94,120]

Regarding pressure control, initial management is by aqueous suppressants. Medical treatment usually fails to control pressure, and surgery is required. Conventional filtration surgery has a high rate of failure. A trial of 5-FU as an adjunct to trabeculectomy did not significantly improve pressure control.[122] Some authors have reported good results with seton procedures.[123]

How Is Glaucoma Complicating Fibrous Ingrowth Managed?

Many eyes with fibrous ingrowth remain quiescent, and periodic observation often reveals maturation of the fibrous scar without progressive damage to the globe. However, if glaucoma does occur, the condition is initially managed with aqueous suppressants. If this fails, filtering surgery is attempted. Blind eyes are best treated with cyclodestructive procedures.[94]

How Is Glaucoma Complicating Siderosis Bulbi Managed?

The pressure elevation is initially managed with aqueous suppressants. If this fails, filtering surgery may be needed. If there is poor visual potential, evidenced by a subnormal or extinguished ERG, cyclodestructive procedures may be more appropriate. In the presence of good visual potential, and decreasing ERG amplitudes on serial testing, removal of the foreign body is needed to limit further retinal damage. However, this may be difficult if the foreign body is encapsulated.

How Is Glaucoma Secondary to Chalcosis Managed?

The pressure elevation is initially managed with aqueous suppressants. If this fails, filtering surgery may be needed. The foreign body is removed by vitrectomy techniques. Cataract extraction and/or vitrectomy may be needed to improve vision.

GLAUCOMA SECONDARY TO CHEMICAL INJURY

Definition

What Is Meant by Glaucoma Secondary to Chemical Injury?

Chemical injury to the eye may be caused by acids or alkalis. Alkaline chemicals, which may penetrate into the anterior chamber within seconds of contact, usually cause more severe anterior segment damage, including anterior segment ischemia. In contrast, acidic chemicals cause coagulation of tissue proteins, which limits the penetration resulting in more superficial injuries, unless the exposure is prolonged and the acid concentration is high. Both types of injury, especially alkali-induced, may be associated with glaucoma.

What Is the Mechanism of Glaucoma Secondary to Chemical Injury?

Immediately after injury, glaucoma may occur due to anterior segment shrinkage[124] and increased uveal blood flow, which may be prostaglandin-mediated.[125] Anterior chamber inflammation, with hypopyon in more severe cases, may develop and contribute to the pressure rise. However, in some cases damage may be so severe as to cause ciliary shutdown, which may result in hypotony.[126]

In the next few weeks to months, there is ongoing repair and scarring, associated with some degree of inflammation. In this phase, pressure elevation may be a result of trabecular meshwork damage that occurred at the time of injury. Glaucoma may also occur as a result of peripheral anterior synechiae formation from inflammation or pupillary block associated with posterior synechiae to the lens. The lens may become cataractous and contribute to the pressure rise by producing pupillary block or by a phacolytic mechanism when lens materials are released.[127]

In later phases, when the repair processes are complete, glaucoma is usually due to trabecular damage and/or the formation of peripheral anterior synechiae.[128]

Epidemiology and Importance

What Are the Settings In Which Chemical Injury Occurs?

Chemical injuries are relatively common. They may occur in the home, most commonly from detergents, disinfectants, solvents, cosmetics, drain cleaners, oven cleaners, ammonia, bleach, and other common household alkaline agents. In an agricultural setting, fertilizer and pesticides tend to be the offending agent. Chemical injuries occurring in industry are usually caused by caustic chemicals and solvents. When strong alkalis and acids are used as an assaultive weapon, the injuries are usually severe. Ocular alkaline injuries are slightly more common than acid injuries.[129]

Diagnosis and Differential Diagnosis

How Is Glaucoma Secondary to Chemical Injury Evaluated?

The following classification is a useful guide for assessment of severity and prognosis of the ocular injury:[129–131]

Grade 1 (good prognosis): Corneal epithelial damage; no ischemia.
Grade 2 (good prognosis): Cornea hazy but iris details seen; ischemia involving at least one-third of the limbus.
Grade 3 (guarded prognosis): Total loss of corneal epithelium; stromal haze blurring iris details; ischemia involving one-third to one-half of the limbus.
Grade 4 (poor prognosis): Cornea opaque, obscuring view of iris and pupil; ischemia involving more than half the limbus.

The depth of penetration is determined clinically by the degree of initial scleral injury, and the subsequent development of cataract and/or hypotony.

The corneal changes due to chemical injury make it difficult to measure the IOP by Goldmann applanation tonometry or Shiøtz tonometry. A Tono-pen or pneumatonometer may be more useful to assess IOP. If the ocular injury is unilateral, these instruments may be calibrated against a Goldmann applanation tonometer in the other eye.[13]

After healing is complete, patients usually have variable degrees of corneal scarring with vascularization, usually associated with conjunctival scarring in the form of symblepharon. This makes it difficult to evaluate the optic disc and visual fields. The consensual reaction of the fellow eye may indicate optic disc damage (or coexisting extensive retinal disease). Ultrasound examination may detect advanced optic disc cupping, although normal ultrasound does not exclude glaucomatous cupping. Visual fields may be evaluated by confrontation, or formal perimetry (static or kinetic) using larger stimuli.[13]

What Is the Differential Diagnosis of Glaucoma Secondary to Chemical Injury?

The differentiation between acidic and alkaline injuries is very important, as the latter tend to be more detrimental to the eye. History taking may reveal the nature of the offending agent. Testing the conjunctival cul-de-sac with litmus paper may be informative.

The combination of high IOP, corneal epithelial ulceration, corneal stromal haze and ulceration, and variable degrees of uveitis up to hypopyon may be caused by microbial keratitis, as well as by chemical injury. In most cases, adequate history taking will immediately differentiate between the two conditions. Furthermore, chemical injury that is severe enough to cause iritis is typically associated with limbal ischemia, which is not usual in the setting of microbial keratitis.

In the late phases, the corneal scarring caused by chemical injury should be differentiated from other causes of corneal scarring such as corneal infection (viral, bacterial, fungal, protozoal) and autoimmune disease such as ocular cicatricial pemphigoid and the Stevens-Johnson syndrome.

Treatment and Management

How Is Glaucoma Secondary to Chemical Burns Managed?

The immediate management of an acute chemical injury is copious irrigation of the eye, together with removal of any material retained in the cul-de-sac. Irrigation is continued until pH testing of the conjunctiva reveals a normal pH. Topical steroids (with antibiotic cover) and cycloplegics are given to treat inflammation. However, topical steroids are used with caution, as they are liable to increase the risk of corneal melting, particularly in the second and third week following injury.[132] Topical citrate, ascorbate and tetracycline may be used to limit collagenolysis.[133] A bandage contact lens is useful to promote reepithelialization.

Management of glaucoma in this early phase of chemical injury is limited to aqueous suppressants and hyperosmotic agents. However, because failure of reepithelialization of the ocular surface may be impaired by topical medications, systemic medications may be preferred. Miotics are relatively contraindicated as they may aggravate anterior segment inflammation, as well as contribute to posterior synechiae that may culminate in pupillary block.[13]

In the intermediate phase of chemical injury (weeks to months), glaucoma may occur due to pupillary block. In such cases, initial management is by vigorous mydriatic-cycloplegic therapy. If this fails to relieve the condition, an Nd:YAG laser iridotomy may be needed. If the cornea is not clear enough to permit laser treatment of the iris, a surgical iridotomy is required. If it is judged that pupillary block is secondary to the lens, cataract extraction is indicated.

In the late phases of chemical injury, the initial management of glaucoma is medical, but filtering surgery may be required. Extensive conjunctival scarring may make conventional filtering surgery impossible, in which case glaucoma shunting procedures (or alternatively cyclodestructive procedures) should be considered.[13]

GLAUCOMA SECONDARY TO RADIATION INJURY

Definition

What Is Meant by Glaucoma Secondary to Radiation Injury?

This is glaucoma secondary to radiotherapy for the treatment of intraocular, periocular, and intracranial neoplasms.

What Is the Mechanism of Glaucoma Secondary to Radiation Injury?

There are several mechanisms whereby radiation can cause glaucoma. Neovascular glaucoma may be caused by radiation-induced iris and anterior chamber angle neovascularization. Hemolytic glaucoma may occur if intraocular hemorrhage complicates radiotherapy of intraocular tumors. Elevated episcleral vein pressure may result from generalized telangiectasia of the conjunctiva after anterior segment irradiation.[134]

Epidemiology and Importance

What Is the Incidence of Glaucoma Following Radiation Injury?

In a series of 169 patients with uveal melanomas treated with local irradiation, neovascular glaucoma occurred in 22 (13%) and was more frequent in eyes with larger melanomas and those exposed to higher radiation dosages.[135]

Diagnosis and Differential Diagnosis

How Is Glaucoma Secondary to Radiation Injury Diagnosed?

Regardless of the type of glaucoma, there will always be a history of irradiation, either for an intraocular tumor (external beam irradiation or brachytherapy), an orbital or eyelid tumor, an intracranial tumor, or a tumor in the head and neck area. In the case of neovascular glaucoma, the pressure rise does not occur immediately after irradiation, and there is typically a latent period between irradiation and the appearance of neovascularization. In contrast, hemolytic glaucoma and glaucoma due to elevated episcleral venous pressure may appear relatively early following irradiation.

Neovascular glaucoma may present with corneal edema if the IOP is in the 50 to 60 mm Hg range. There is usually flare in the anterior chamber, and new vessels are seen on the iris. Gonioscopy will reveal new vessels in the angle; the angle may be open or there may be broad peripheral anterior synechiae. Fundus examination may show evidence of an ablated intraocular tumor and/or radiation retinopathy (retinal hemorrhages, microaneurysms, cotton-wool spots, optic disc, or retinal neovascularization).

If the cause of IOP elevation is hemolytic glaucoma, there will be signs of hyphema or vitreous hemorrhage. Red-brown cells (macrophages laden with hemolytic debris) may be seen in the anterior chamber, and if excessive, may deposit on the angle, especially inferiorly (see above).

Glaucoma due to raised episcleral venous pressure is suspected when there is no intraocular cause of glaucoma together with dilatation and telangiectasia of the episcleral vessels. Gonioscopy may reveal blood in Schlemm's canal.

What Is the Differential Diagnosis of Glaucoma Secondary to Radiation Injury?

The differential diagnosis of neovascular glaucoma, hemolytic glaucoma, and glaucoma secondary to elevated episcleral venous pressure is discussed elsewhere in this book.

Treatment and Management

How Is Glaucoma Secondary to Radiation Injury Managed?

Regardless of cause, glaucoma secondary to radiation injury is initially managed with aqueous suppressants. In the case of neovascular glaucoma, steroids and cycloplegics are also needed to control the associated iritis, whereas miotics are avoided as they may aggravate the iritis by increasing leakage from new vessels. The definitive management of neovascular glaucoma, hemolytic glaucoma, and glaucoma secondary to elevated episcleral venous pressure is discussed in Chapters 6, 13 and 14.

GLAUCOMA SECONDARY TO ELECTRICAL INJURY

Definition

What Is Meant by Glaucoma Secondary to Electrical Injury?

This is a typically transient pressure rise that has been reported following accidental and therapeutic electrical injury such as electroshock therapy and cardioversion.[136–138]

What Is the Mechanism of Glaucoma Secondary to Electrical Injury?

The pressure spike that occurs after electrical injury may be related to release of pigment from the iris pigment epithelium. Venous dilatation and contraction of the extraocular muscles also may be involved in the pathogenesis of glaucoma.[13]

Epidemiology and Importance

How Common Is IOP Rise After Electrical Injury?

Glaucoma secondary to electrical injury is typically a transient condition, and it may or may not leave signs in the eye. Therefore, its true incidence is unknown.

Diagnosis and Differential Diagnosis

How Is Glaucoma Secondary to Electrical Injury Diagnosed?

There is usually a history of either accidental electrical injury or therapeutic electrical injury in the form of cardioversion or electroconvulsive therapy. By the time the patient is seen, the IOP may be normal. The only sign of previous injury may be loss of pigment from the iris pigment epithelium evidenced by transillumination defects in the iris seen on retroillumination. There may be dispersed iris pigment on the anterior capsule of the lens, the iris, and the corneal endothelium. Gonioscopy may also reveal pigment dispersion on the angle.

What Is the Differential Diagnosis of Glaucoma Secondary to Electrical Injury?

Transient glaucoma associated with pigment dispersion may also be seen in other conditions such as pigmentary glaucoma, uveitis, and the pseudoexfoliation syndrome. The differential diagnosis of pigmentary glaucoma is discussed in Chapter 9.

Treatment and Management

How Is Glaucoma Secondary to Electrical Injury Managed?

Due to the transient nature of the condition, treatment is seldom required.

GLAUCOMA SECONDARY TO THERMAL INJURY

Definition

What Is Meant by Glaucoma Secondary to Thermal Injury?

This is glaucoma secondary to thermal injury of the eye, usually caused by house fires and flash fires of combustible vapors and gases.

What Is the Mechanism of Glaucoma Secondary to Thermal Injury?

Glaucoma is usually associated with severe facial burns involving the eyelids. The main underlying mechanism is increased orbital pressure from orbital congestion.[139] Severe burns are associated with shift of water from the intravascular to the extravascular space,[140] particularly to the periocular extravascular space, which can cause swelling and tightness of the eyelids. This shift of fluid from the intravascular compartment may cause dangerous hypotension and hemoconcentration. Therefore, the administration of large quantities of intravenous fluids in severely burned patients is essential to maintain blood pressure. This is an additional factor contributing to orbital congestion. It is also possible that the IOP increases secondary to pupillary block caused by orbital pressure on the globe, displacing the lens anteriorly.[139]

Typically, the severely burned patient does not develop periorbital edema until a few hours after the injury. Therefore, early after the injury, the IOP may be normal, only to rise once orbital congestion sets in.

Epidemiology and Importance

What Are the Risk Factors for Glaucoma Secondary to Thermal Injury?

The main risk factor for glaucoma after thermal injury is the occurrence of orbital congestion, which is more liable to occur in association with facial burns, but may also occur in severe burns sparing the face.

Diagnosis and Differential Diagnosis

How Is Glaucoma Secondary to Thermal Injury Diagnosed?

In most cases, the severely burned patient is seen by the ophthalmologist in an emergency room or a burns unit, and the patient may not be amenable to full examination. On arrival at the hospital, some severely burned patients are able to cooperate for ocular examination, possibly to relate previous ocular problems and to permit visual acuity testing with a near-vision test card. Other patients are pharmacologically paralyzed and given mechanical pulmonary ventilation shortly after arrival, which limits cooperation for examination even though they may be fully conscious and aware.

The eyelids may show partial- or full-thickness burns, and the eyelashes may be singed. The conjunctiva may be chemotic, and the cornea may show epithelial defects. If there is orbital congestion, eyelid retraction may be necessary for examination of the eye. After the cornea has been examined, tonometry is performed with retraction relaxed to permit a more accurate reading. Topical anesthesia should be used because the patient may have full sensation even though unable to communicate.

Periorbital edema does not set in until a few hours after the injury. Furthermore, periorbital edema may occur even if the face is spared from a direct burn. Therefore, if the patient is found to have a normal IOP, examination should be repeated a few hours later so as not to miss an IOP rise associated with delayed orbital congestion.[139]

Treatment and Management

How Is Glaucoma Secondary to Thermal Injury Managed?

The immediate management of a severely burned patient with ocular injury consists of irrigation of the eyelids and conjunctival sacs to remove any particulate material. Singed eyelashes are removed with a moist sponge to prevent them from entering and irritating the eyes. Burned skin is treated with silver sulfadiazine when there is no known allergy to sulfonamides. Sulfacetamide ophthalmic ointment may also be applied to the globes. In general, aminoglycosides are best avoided to lessen the chance of emergence of resistant strains.

If the IOP is found to be high in association with severe periocular edema, lateral canthotomy is indicated. If possible, local anesthesia should be injected through unburned skin. Canthotomy wounds are treated with an ophthalmic antibiotic ointment.[139]

Future Considerations

What Are the Future Considerations for Traumatic Glaucoma?

Traumatic glaucoma is largely a preventable disease. Protective eyewear can effectively reduce the incidence of ocular trauma, both in sports and in workplaces. In an epidemiologic study of eye injuries sustained by 59 professional basketball players, 57 players (96.6%) were not wearing protective eyewear at the time of injury.[141] In the United States, it is estimated that close to 1,000 eye injuries occur daily in American workplaces; up to 90% of these injuries could be prevented by the use of protective eyewear.[142] Eye injuries related to assault are more difficult to prevent than eye injuries occurring in other settings. Public health efforts to reduce the use of alcohol, drugs, and firearms may reduce the incidence of injuries related to assault.[3]

If eye trauma does occur, it is preferable to refer the patient to a specialized eye trauma center. In the United States, there are several eye trauma centers

nationwide that report to the National Eye Trauma System, which was "developed to provide optimal clinical care for severe ocular injuries, to foster research on eye injury, and to increase awareness of ocular trauma as a public health problem."[143] This may a serve as a model for more effective management of eye trauma.

Finally, the development of new antiglaucoma medications (such as prostaglandin agonists) may increase the options available for medical management of traumatic glaucoma.

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◆ 14 ◆

Neovascular Glaucoma

Cuong D. Vu and John J. Alappatt

Definition

How Is Neovascular Glaucoma Defined?

Neovascular glaucoma (NVG) is a type of secondary angle glaucoma attributed to new blood vessel formation in the angle. It is the end stage of a variety of ophthalmic disorders whose common feature is widespread retinal hypoxia (Table 14-1).

Epidemiology and Importance

Why Is Prompt Recognition and Treatment of NVG Important?

NVG is a serious complication with significant potential for devastating visual loss. Once in its fulminant stage, the likelihood for successful outcome is markedly reduced. The best visual outcomes occur with prompt recognition of this complication in its earliest stages and proper treatment of the underlying etiology.[1]

What Are the Demographic Characteristics of Patients Who Develop NVG?

There is no age, gender, race, or ethnic group predilection for the development of NVG. Because close follow-up examination is a key factor in the detection of the early stages of NVG, patient compliance is a major factor.

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Table 14–1 Disorders Predisposing to NVG

Systemic vascular disease
Carotid occlusive disease
Carotid cavernous fistula
Giant cell arteritis
Sickle cell disease
Ocular vascular disease
Diabetic retinopathy
Central vein occlusion
Central artery occlusion
Branch vein occlusion
Coats' disease (retinal telangiectasia)
Eales' disease
Retinopathy of prematurity
Persistent hyperplastic primary vitreous
Anterior segment ischemia
Other ocular disease
Chronic uveitis
Chronic retinal detachment
Primary rhegmatogenous
Sticklers' syndrome
Retinoschisis
Trauma
Endophthalmitis
Intraocular tumor
Uveal melanoma
Metastatic carcinoma
Retinoblastoma
Therapy
Radiation treatment
Postvitrectomy diabetic eye

What Are the Biologic Characteristics of Patients Who Have NVG?

There is no particular blood level of antibodies, chemicals, enzymes, or cellular constituents that is diagnostic of NVG. However, patients may demonstrate systemic features consistent with their underlying etiology. Diabetics may be poorly controlled with elevated serum glucose. Patients with carotid occlusive disease often have concomitant heart disease, hypertension, and significant obstruction on carotid Doppler testing. Glaucoma is a risk factor for central retinal vein occlusion (CRVO).

What Are the Social And Economic Factors of Patients Who Have NVG?

Effective prevention and treatment of NVG is dependent on timely diagnosis and management. Thus, social and economic factors predisposing to poor compliance and follow-up must be considered.

What Are the Personal Habits of Patients Who May Develop NVG?

There are no personal habits such as tobacco use, diet, or physical exercise likely to contribute to the development of NVG. A history of noncompliance with medical treatment is a risk factor for late detection of NVG.

What Are the Genetic Characteristics of Patients Who May Develop NVG?

There are no genetic characteristics that favor the development of NVG.

What Are The Major Entities that Lead to NVG?

The medical literature contains many possible etiologies to consider in patients with NVG, but diabetes mellitus, CRVO, and ocular ischemic syndrome (OIS) are the primary underlying diseases to consider. There are two large epidemiologic studies on the causes of NVG (Table 14-2). The Madsen[2] study reviewed hemorrhagic glaucoma in 70 patients in a Denmark eye facility. The Brown et al[3] study is a retrospective review of 208 patients with NVG in a major urban eye hospital.

What Is the Pathogenesis of NVG?

NVG is a complication thought to be secondary to angiogenic factors produced by the ischemic retina that enter the anterior chamber.[1] Various substances have been suggested as the underlying common agent. Of note, vascular endothelial growth factor (VEGF) has been shown to induce a noninflammatory iris neo-

Table 14–2. Etiology of NVG in Epidemiologic Studies

Author and Year	No. of Patients	Central Retinal Vein Occlusion	Diabetic Retinopathy	Ocular Ischemic Syndrome	Comments
Madsden, 1971[2]	70	37%	43%	N/A	20% were "miscellaneous"
Brown et al, 1984[3]	208	36%	32%	12.9%	97% had extensive retinal ischemia that preceded the onset of NVI

vascularization in nonhuman primate eyes when injected at a concentration comparable to that found in human eyes with neovascular glaucoma.[4] There is evidence that the angiogenic factor originates from the posterior segment of the eye. NVG has been observed following noncomplicated laser posterior capsulotomy, which presumably permitted angiogenic factors access to the anterior chamber.[5] Additionally, neovascularization of the iris (NVI) has been observed to begin at the peripheral iridotomy site in a patient with iris bombé.[6]

Diagnosis and Differential Diagnosis

How Is NVG Diagnosed?

In the classic presentation of fulminant NVG, patients complain of pain, photophobia, and decreased vision. Visual acuity is typically in the hand motion to counting fingers range. The secondary closed angle results in extremely high intraocular pressure (IOP), producing conjunctival injection, steamy cornea, and inflammation. Slit-lamp examination demonstrates NVI and ectropion uvea (a flattened iris anterior face and rotation of the iris pigment epithelium anteriorly). Gonioscopy reveals angle closure, with the inferior portion being the last to seal off. Fundus examination often shows an ischemic retina and thus the underlying disorder.

There may be great variability in clinical presentation in each individual case of NVG. For example, IOP may be normal or reduced in NVG secondary to OIS.

How Is NVI Differentiated from Normal Iris Vasculature?

Abnormal iris vessels have characteristic features that differentiate them from normal iris vessels. Normal iris vessels have a nonarborized intrastromal orientation. Iris neovascularization first appears as buds of vessels, resembling glomeruli. These buds are typically detected first at the pupillary margin. Later stages of NVI show a fine net of blood vessels in an extrastromal location. NVI typically demonstrates angiographic leakage, whereas normal iris vessels do not leak. Any blood vessels that cross the sclera spur are considered abnormal. Later stages lead to arborization into the trabecular meshwork, giving the meshwork a red appearance. It may be difficult to differentiate engorged iris vessels in an inflamed eye from NVI.

How Does the Neovascularization of the Angle Lead to Angle Closure?

Posterior segment hypoxia leads to the production of angiogenic factors that circulate into the anterior segment, stimulating the growth of new blood vessels, usually first at the pupillary margin. It is classically thought that neovascularization of the angle (NVA) does not occur without accompanying NVI, though there are anecdotal accounts that dispute this claim. For example, gonioscopy may detect NVA prior to the detection of NVI.[7]

Pathologic studies have confirmed the presence of an accompanying "invisible" fibrovascular membrane in cases of NVG. Contraction of this fibrovascu-

Table 14–3. Differential Diagnosis of Early NVG and Characteristic Features

Disease	Characteristic Features
Fuchs' heterochromic iridocyclitis	White, quiet eyes Fine, fragile blood vessels may cross scleral spur Synechiae do not develop No associated retinal ischemia
Pseudoexfoliation glaucoma	Target lesion on anterior capsule No associated retinal ischemia
Uveitis	No associated retinal ischemia Iris vascularization regresses with steroid treatment No NVA

lar membrane leads to points of synechial angle closure. Coalescence of these points of synechial closure ultimately leads to total angle closure and thus dramatic reduction of trabecular outflow. The progression of NVI to NVA to NVG may occur over days, weeks, months, or years.

What Is the Differential Diagnosis of NVG?

In its early stages, NVG must be differentiated from other disorders with prominent iris blood vessels. There are a number of historical and clinical features that may facilitate this distinction (Table 14-3).

In the fulminant stage, the main differential diagnosis to be considered is acute primary angle closure because it shares with NVG the common features of poor vision, extreme pain, high IOP, congested conjunctiva, and steamy cornea. If examination of the fellow eye also reveals a narrow occludable angle, then a diagnosis of primary angle closure is more likely. Also, pressure on gonioscopy (compression gonioscopy) may force the angle open. In NVG, the angle is sealed and cannot be forced open. Funduscopic exam in NVG is consistent with a hypoxic posterior segment.

What Are the Key Distinguishing Features of the Main Causes of NVG?

This chapter discusses differentiating between the most likely entities in patients with NVG (Table 14-4). Chapter 11 discusses the primary etiologies of central retinal vein occlusion, diabetes mellitus, and OIS.

Treatment and Management

What Are the General Principles to Consider in Preventing Progression to NVG?

It is crucial to maintain a high clinical suspicion for the potential of the currently managed disease to progress to this complication (Fig. 14-1). Prompt recognition of iris neovascularization is critical to successful management. This is best achieved with standardized high-magnification nondilated examination of the iris, with particular attention to the pupillary margin.

Table 14–4. Differential Features of the Predominant Etiologies of NVG

Feature	Ocular Ischemic Syndrome	Central Retinal Vein Occlusion	Diabetic Retinopathy
Laterality	80% unilateral	Unilateral	Bilateral
Age at presentation (years)	50–80	50–80	Variable
Retinal veins	Dilated, beaded	Dilated, tortuous	Dilated, beaded
Retinal arteries	Narrow	Normal	Normal or narrowed
Optic disc	Normal	Edema	Normal
Hard exudates	Absent	Rare	Common
Retinal hemorrhages	Dot/blot, midperiphery	May be severe, entire retina, four quadrants	Mostly midperiphery and posterior pole
Microaneurysms	Midperipheral	Variable	Limited to posterior pole
Retinal artery perfusion pressure	Decreased	Normal	Normal
FA: choroidal filling time	Delayed, patchy	Normal	Normal
FA: arteriovenous transit time	Prolonged	Prolonged	Normal
FA: retinal vessel staining	Mainly arterial	Venous	Absent
Other	Carotid bruit, hypertension, atherosclerosis	Hypertension, glaucoma	Renal failure, peripheral neuropathy

FA, fluorescein angiography.

When NVI is detected, determine and treat the underlying cause of posterior segment hypoxia. If examination reveals a fundus without definite hypoxia, always consider the diagnosis of OIS. The goal is to reduce posterior segment hypoxia and thus regress the NVI and NVA before it reaches fulminant NVG.

What Are the Techniques Used to Prevent Progression to NVG?

Panretinal photocoagulation is the preferred means of decreasing posterior segment hypoxia, but it is limited because successful treatment is largely dependent on clear media. Topical glycerin may be used to decrease corneal edema so that one may achieve sufficient improved view for effective treatment. The goal of treatment is to ablate the ischemic retina. Insufficient treatment will not adequately reduce the hypoxic drive to NVG progression. The effectiveness of panretinal photocoagulation in NVI and NVG has been well documented.[8,9]

Panretinal cryotherapy may be useful in cases where the cornea, lens, or vitreous is too hazy to get adequate laser treatment. The disadvantage of this

technique is that it promotes significant breakdown of the blood–retina barrier, stimulating inflammation.

Goniophotocoagulation is a laser treatment directly applied to the iris and angle to reduce NVI and NVA. The effectiveness of this technique is not established. The only documented cases of successful goniophotocoagulation have been performed in conjunction with panretinal photocoagulation.[10] In fact, goniophotocoagulation may precipitate inflammation and hasten synechial angle closure.

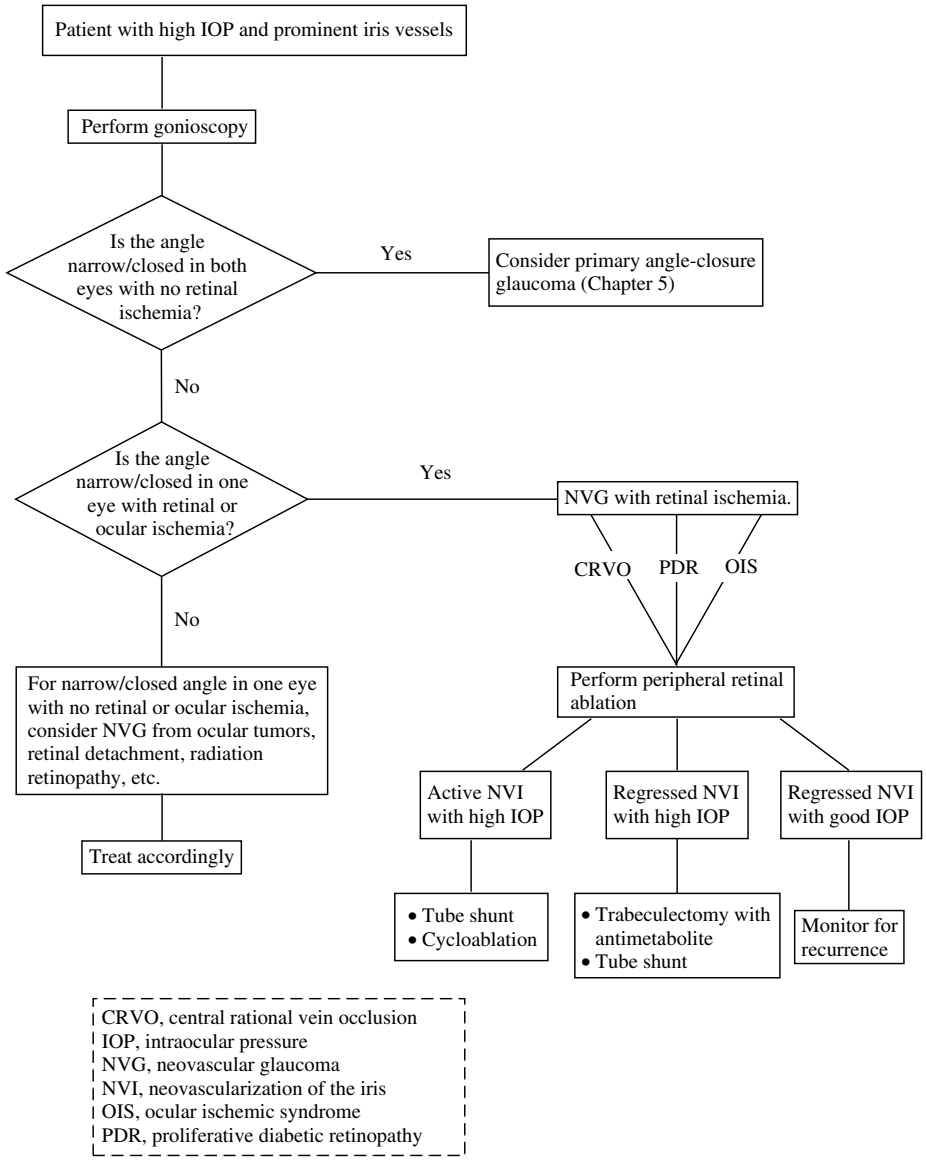

Figure 14–1. Algorithm for managing a patient with NVG.

How Is a Patient with Diabetic Retinopathy Prevented from Progressing to NVG?

Prompt panretinal photocoagulation should be employed when high-risk proliferative features are found in diabetic eyes. The Diabetic Retinopathy Study demonstrated that vitreous hemorrhage, disc neovascularization, and new areas of retinal neovascularization are ominous features of proliferative diabetic retinopathy.[11]

Particular caution should be employed in diabetic patients who are status post-cataract surgery or postvitrectomy, as they may quickly progress to fulminant NVG. It is thought that preservation of the posterior capsule during cataract surgery minimizes the risk of worsening retinopathy. The incidence of NVG complicating vitrectomy has been decreasing, presumably due to better equipment and endolaser treatment.[12] Systemic features such as hypertension and renal failure are often found concomitantly in diabetics who progress to NVG.

How Is a Patient with Newly Diagnosed CRVO Prevented from Progressing to NVG?

Important data regarding the history of treated and untreated CRVO have been reported by the CRVO study group.[13] Particular observations to consider include:

1. One-third of initially perfused CRVO may progress to ischemia over 3 years.
2. Initially nonperfused CRVO is at 35% risk of developing NVI/NVA.
3. Panretinal photocoagulation should commence when NVI/NVA develops.

Differentiating between ischemic and nonischemic status may be difficult secondary to retinal obscuration by retinal hemorrhage. Poor visual acuity, presence of an afferent pupillary defect, and decreased electroretinogram values have also been reported to be predictive of progression to neovascular disease.[14] Recommended follow-up schedules may be guided by visual acuity at presentation, as per the guidelines of CRVO study group's report:

- 20/40 or better: every 1 to 2 months for the first 6 months;
- 20/50 or worse: every month for the first 6 months;
- worsening visual acuity: an ominous sign of progression to ischemic status.

Undilated gonioscopy should be done at each follow-up exam because NVA may develop prior to NVI.[7]

How Is a Patient with OIS Prevented from Progressing to NVG?

Always consider this diagnosis in cases when the funduscopic exam does not show profound clinical evidence of retinal ischemia or when panretinal photocoagulation does not regress NVI/NVA. Some studies report that only a third of these patients have elevated IOP.[1] This decrease in aqueous production is thought to be due to hypoperfusion of the ciliary body. Panretinal photocoagu-

lation should be the first step, though it may not be effective, because OIS also gives rise to anterior segment ischemia late in its course.[15] Once surgical revascularization of the carotid occurs, it may lead to an increase in IOP and worsened ophthalmic vessel disease. Internal medicine or cardiology services should be consulted in these patients to rule out carotid disease and concomitant cardiovascular disease.

The Underlying Cause of the NVG Was Diagnosed and Treated and the IOP Is Now Within Normal Limits. What is Next?

Close monitoring and observation are essential because this condition may recur at any time.

What Treatment Options Are Available If the IOP Is Still Elevated Following Complete Treatment of the Underlying Cause of NVG?

The IOP may still be elevated because despite inducing the NVI/NVA to quiescence, the angle is still zipped shut and a permanent angle closure status is maintained. Medical therapy is the preferred means of controlling IOP at this point.

Ocular pressure reduction medications may also be used to obtain a clearer view for diagnostic and treatment purposes. The aim is to maintain acceptable IOP. Avoid pilocarpine and other cholinergics, because they may break down the blood vessel barrier and facilitate increased inflammation. Topical corticosteroids are helpful in reducing inflammation and may be used as indicated.

What Treatment Options Are Available If, Despite Maximally Tolerated Antiglaucoma Medications, the IOP Is Still Elevated?

NVG typically responds poorly to conventional glaucoma surgery. These poor outcomes have prompted a variety of different interventions strategies. The main approaches used are trabeculectomy with antimetabolites, tube-shunt surgery, cyclocryotherapy, and cyclophotocoagulation. In an eye with quiescent neovascularization, trabeculectomy with antimetabolites is considered by many to be the primary option. If there are active vessels present, tube-shunt versus ciliary body ablation is considered (see Chapter 19).

What Are the Data Regarding Success Utilizing Trabeculectomy?

Trabeculectomy without metabolite and without concomitant retinal ablation has a low rate of NVG regression (10–30%), whereas, with panretinal photocoagulation as a preoperative adjunct, a 67% success rate has been reported at 12-month follow-up.[16]

What Is the Long-Term Success of Trabeculectomy with 5-Fluorouracil (5-FU)?

A retrospective case study of 34 NVG eyes treated with 5-FU and trabeculectomy showed adequate IOP control decreased over time. At 1-year follow-up, 70% were controlled, whereas at 5 years the control rate was only 28%.[17] Risk factors identified with poor prognosis in this study included insulin-dependent diabetes mellitus and age younger than 50 years.

What Are the Success Rates of Utilizing Tube-Shunt Surgery for NVG?

The single-plate Molteno has been documented with a satisfactory IOP control rate of about 60% at 1 year and 10% at 5 years.[18] Another retrospective study showed that the Baerveldt implant yielded 79% success at 12 months but only 56% after 18 months.[19] In both of these studies, success was defined as a final IOP of 6 to 21 mm Hg without the need for additional surgery and without devastating complication.

What Is More Effective in the Management of NVG, Tube-Shunt Surgery or Neodymium:Yttrium-Aluminum-Garnet (Nd:YAG) Cyclophotocoagulation?

In a retrospective case-matched comparative study of 49 patients, satisfactory IOP control was achieved in 66% of tube shunted patients versus 38% of cyclophotocoagulated patients.[20]

Future Considerations

What Are the Future Considerations in Managing NVG?

Transscleral diode cyclophotocoagulation has emerged as an effective means of lowering IOP in refractory glaucoma. There have been reports of success utilizing diode cyclo and retinal ablation in cases where the view is compromised.[21] Threlkeld et al[22] noted that diode cyclophotocoagulation for eyes with NVG appeared to have a higher risk of hypotony. Only limited case series are currently available for this technique. There has been a recent report that interleukin-6 is present in the aqueous humor of patients with NVG secondary to CRVO.[23] Future modification of the inflammatory factors seen in NVG may provide a new means of imaging NVG.

Acknowledgment

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◆ 15 ◆

Drug-Induced Glaucoma

Robert M. Mandelkorn

Definition

How Do You Define Drug-Induced Glaucoma?

Some patients develop glaucoma from medications administered directly to the eye or systemically within the body. These medications can in turn be further subdivided into those drugs that have a steroidal component and those that do not. This chapter defines and classifies those glaucomas felt to be associated with medication, whether it be a corticosteroid or nonsteroidal medication (Fig. 15–1).

What Is Corticosteroid-Induced Glaucoma?

The most readily recognized medications associated with glaucoma are the corticosteroids. In most cases, glaucoma is found to be associated with a topically administered medication in the form of an eyedrop or an ointment.

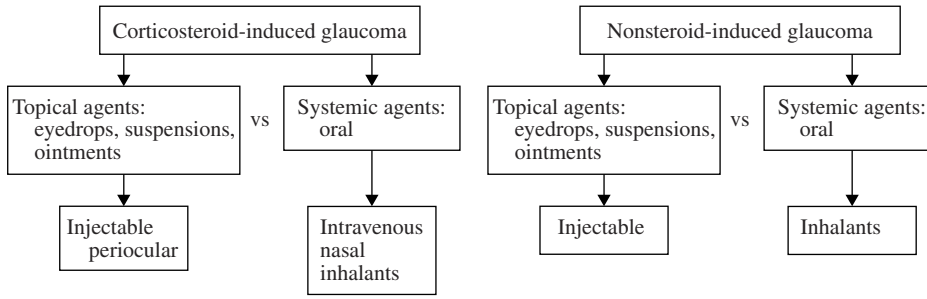

Figure 15–1. Drug-induced glaucoma: classification.

Clinical Pathways in Glaucoma. Edited by Zimmerman and Kooner.
Thieme Medical Publishers, Inc., New York © 2001.

However, it can also be observed with an alternative form of administration of the medication to the eye, such as in the case of periocular injection to the eye. In addition, systemic administration of steroids has also been well documented to produce glaucoma in the susceptible patient. Glaucoma is also observed in Cushing's syndrome with the production of excess endogenous steroids.

The issue of corticosteroid-induced glaucoma was first raised in the 1950s with the observation of glaucoma in association with both the systemic administration of adrenocorticotropic hormone (ACTH)[1] and cortisone,[2] as well as with topical administration of cortisone.[3,4]

Subsequently, both Becker and Chevrette[5] and Armaly[6] reported an association between patients with open-angle glaucoma and topical corticosteroids. An attempt was made by these authors to seek a genetic linkage between corticosteroid sensitivity and glaucoma. Subsequent authors have not shown this linkage to occur.[7–10]

Epidemiology and Importance

What Is the Epidemiology of Corticosteroid-Induced Glaucoma, and Which Patient Is At Risk?

Armaly[11] and Becker[12] have shown that within the general population 5 to 6% of healthy subjects will develop marked elevation of intraocular pressure (IOP) 4 to 6 weeks after chronic administration of topical dexamethasone or betamethasone eye drops. These studies have also shown that these numbers are directly related to the frequency of administration and duration of usage of this medication, with increasing usage related to increased risk of elevated IOP.

At higher risk are patients with primary open-angle glaucoma,[13,14] their first-degree relatives,[8,15,16] diabetic patients,[17] highly myopic individuals,[18] and patients with connective tissue disease,[19] specifically rheumatoid arthritis (Table 15–1).

In addition, patients with angle recession glaucoma are more susceptible to corticosteroid-induced glaucoma.[20]

When Is the Risk Greatest?

Traditional thinking has been that there is a grace period of 4 to 6 weeks before an elevated IOP may be observed. This time period is dependent on the individual susceptibility of the eye at risk and may vary from 2 weeks to months to

Table 15–1. Risk Factors for Corticosteroid-Induced Glaucoma

Primary open-angle glaucoma[13,14]
First-degree relative of patient with primary open-angle glaucoma[8,15,16]
Diabetes mellitus[17]
High myopia[18]
Connective tissue disorder[19] (sp. rheumatoid arthritis)
Angle recession glaucoma[20]
Cushing's syndrome[34,35]

years after the corticosteroid preparation has begun, requiring the clinician to be on constant guard and checking the patient on a regular basis.

In the patient with a history of steroid-induced glaucoma, this elevation of IOP may occur within 2 weeks of initialization of a corticosteroid preparation to the eye, whereas in an otherwise normal eye it may not occur until years later.

What Is the Risk with Differing Corticosteroid Preparations?

Although it has been shown that any corticosteroid preparation can produce an elevated IOP, the greatest risk is observed with the most potent steroidal preparations (Table 15–2). Fluoromethalone (FML) and medrysone are less potent topical corticosteroids, but they have also been shown to produce an elevated IOP.[22, 27] However, it must be noted that the risk of producing an elevated IOP with these medications is much less than with the former medications listed above.

Newer corticosteroid preparations include rimexolone (Vexol) and loteprednol etabonate (Lotemax, Alrex). The risk of producing an elevated IOP with these agents[23,26] is comparable to FML.[27]

What Is the Route of Corticosteroid Administration?

The picture of corticosteroid-induced glaucoma is most commonly observed with topically administered corticosteroids in the form of eye drops or ointments. This condition can also be observed when corticosteroids are given periocularly in either subconjunctival,[28] subtenon[29] or retrobulbar injection, [30] especially in a depot preparation[24] (Table 15–2).

An elevated IOP and glaucoma can also be observed to occur, though less commonly, when corticosteroid preparations are give systemically,[2,25] when skin preparations in the form of lotions and creams are placed near the eye[31] or applied to sites remote from the eye,[32] and with inhaled steroids, such as those used in the treatment of asthma.[21] It should also be noted that there appears to be an additive effect to corticosteroid usage when used both topically and systemically.[33]

Table 15–2. Available Steroid Preparations

High Risk	Low Risk
Beclomethasone dipropionate[21] (nasal and/or inhalant preparation)	Rimexolone (Vexol)[26]
Dexamathasone[5,6]	Loteprednol etabonate (Lotemax, Alrex)[23]
Betamethasone[22]	Fluoremethalone (FML)[27]
Prednisone[23]	Medrysone (HMS)[22]
Triamcinolone acetonide[24] (in depot preparation)	
Cortisone (oral[2] and/or intravenous[25] preparation)	

Finally, in the patient producing endogenous corticosteroids, such as in the patient with adrenal hyperplasia[34]or Cushing's disease,[35] an elevated IOP may also be observed.

What Is the Mechanism of Action for Corticosteroid-Induced Glaucoma?

To most authors, the mechanism of action for the increased IOP observed in these patients is felt to be due to an increased resistance to aqueous humor outflow[36,37] through the trabecular meshwork rather than an increased production of aqueous humor.

Within the trabecular meshwork, an accumulation of polymerized glycosaminoglycans[38–40] can be observed in these eyes. Several authors have felt that this finding represents the stabilization of lysosomal membranes by corticosteroids.[41,42] In addition, increased collagen,[43] elastin,[44] and fibronectin[45] have been observed within the extracellular matrix in these eyes. A sialoglycoprotein has also been observed in these eyes.[46]

Other authors have felt that the presence of corticosteroids may produce a reorganization of the cytoskeleton within the trabecular meshwork cells, resulting in the above-mentioned changes observed in these cells.[47,48]

Whatever may eventually be shown to be the cause of this observed IOP rise in these eyes, it appears to reflect a change in the basic functioning of the trabecular meshwork cells[49,50] which alters the resistance to outflow of aqueous humor through these cells. This change in the basic physiologic appearance and functioning of the trabecular meshwork cells is reflected in the initial clinical appearance of the patient. Indeed, the patient usually presents with white and quiet eyes with no evidence of pain or discomfort.

Diagnosis and Differential Diagnosis

What Is the Differential Diagnosis of Corticosteroid-Induced Glaucoma?

The differential diagnosis includes open-angle glaucoma and ocular hypertension. In those patients with a prior history of steroid usage, the differential diagnosis should include normal pressure glaucoma. In those patients with occludable angles, the differential diagnosis should include chronic angle-closure glaucoma. Finally, in the pediatric patient the differential diagnosis should include congenital glaucoma (Table 15–3).

Table 15–3. Differential Diagnosis of Corticosteroid-Induced Glaucoma

Open-angle glaucoma
Ocular hypertension
Normal pressure glaucoma
Chronic angle-closure glaucoma
Congenital glaucoma

What Are the Symptoms of Corticosteroid-Induced Glaucoma?

Occasionally, the patient may complain of intermittent blurring of vision if the IOP has risen to the point of compromising corneal function or if sufficient damage has occurred to the ocular nerve from the elevated IOP.

In addition, the patient may also complain of blurred vision from cataracts, which classically are posterior subcapsular.[51] Additional findings at the time of initial presentation may include ptosis,[37] mydriasis,[37] atrophy of the eyelid skin,[31] ocular infections,[31] delayed wound healing, corneal ulcers, and conjunctival necrosis,[52,53] the latter occurring following subconjunctival corticosteroid administration.

How Is the Diagnosis of Corticosteroid-Induced Glaucoma Made by the Clinician?

The diagnosis can be made only by questioning the patient. A careful history should include any medications prescribed by the primary care physician, especially corticosteroid eye drop preparations for the treatment of red eye. Most striking is that patients may not volunteer that they are taking corticosteroids in any form.

How Is the Diagnosis of Nonsteroidal Drug-Induced Glaucoma Made by the Clinician?

It behooves the clinician to have a healthy dose of suspicion and to carefully seek from the patient a complete list of all medications being taken, including both prescription and nonprescription agents.

Treatment and Management

How Is Corticosteroid-Induced Glaucoma Treated?

Once the diagnosis has been made, the most obvious solution is to have the patient stop using the offending corticosteroid. Although it may be possible to do this in many cases, the clinician may be forced to either substitute an alternative corticosteroid[54] or to prescribe an alternative agent, such as a nonsteroid antiinflammatory drug (NSAID)[55] (Fig. 15–2).

Where the offending corticosteroid can be stopped,[24] this step may be enough to alleviate the problem. Unfortunately, in some cases, it is not enough, and the elevated IOP may not be relieved by the patient's stopping the use of the corticosteroid.[40] In addition, in those eyes where the corticosteroid cannot be stopped, additional treatment will be required.

If the IOP is still elevated, medical therapy may be required to lower it. In such instances, the first line of therapy appears to be the use of topical beta-blockers, where there is no contraindication such as pulmonary or cardiac problems or a history of allergy to beta-blockers.

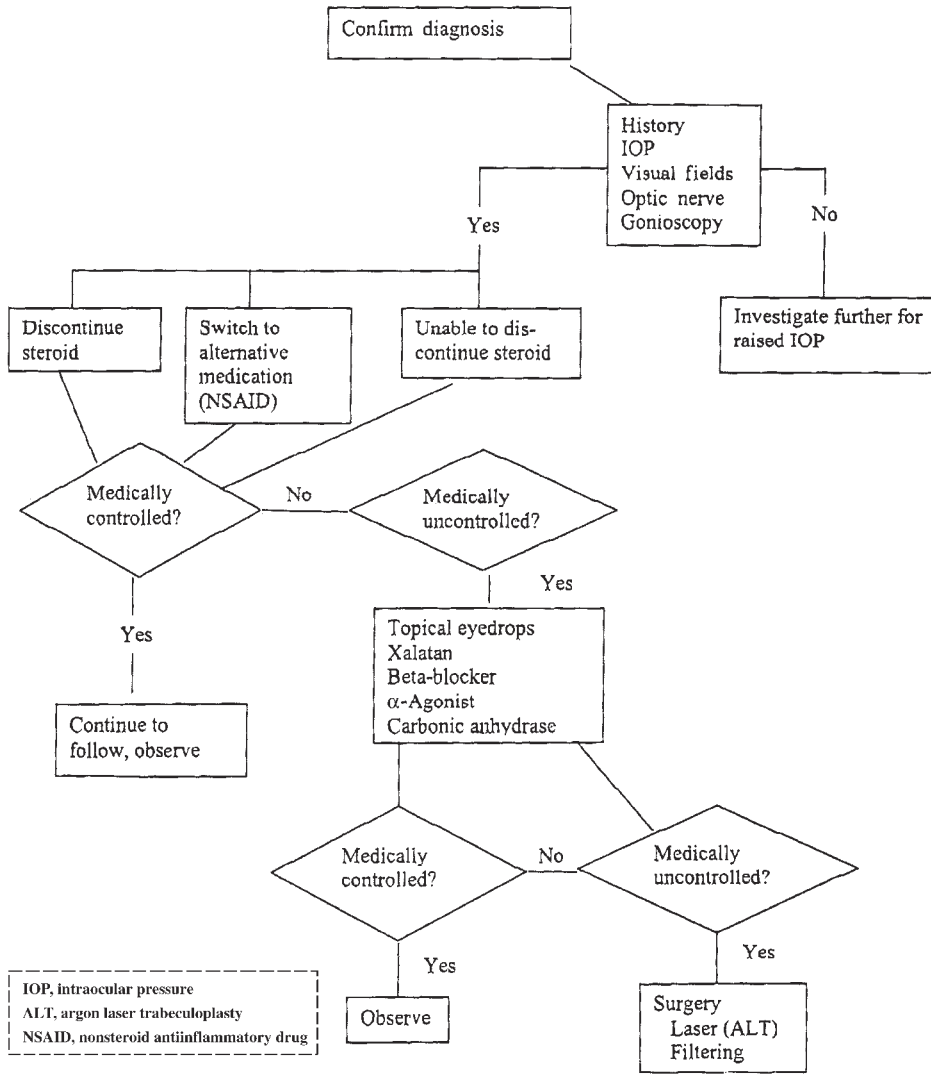

Figure 15–2. Algorithm for management of corticosteroid-induced glaucoma.

Other agents, such as carbonic anhydrase inhibitors and α-alpha agonists, may also be helpful in these eyes. Although miotic agents, epinephrine products, and prostaglandins are helpful in the treatment of elevated IOP, they should be used with caution in these patients, especially if there is an underlying history of ocular inflammation, which may have been the underlying reason for initially using corticosteroid agents. Also, there will be patients who are unresponsive to medical therapy. In these patients, argon laser trabeculoplasty (ALT) may be helpful, if not, filtration surgery may be required to alleviate the elevated IOP (Fig. 15–2). Although these measures may be required to save these eyes, it should also be kept in mind that many of these treatment options can be avoided by careful observation of these patients once they have been started on any corticosteroid regimen.

What Nonsteroidal Agents Are Associated with Glaucoma?

Unlike corticosteroid agents, the list of nonsteroidal agents associated with glaucoma is wide and diverse (Table 15–4). The causes of glaucoma associated with these agents are also just as varied (Fig. 15–3).

The largest single cause of glaucoma in these patients appears to be an atropine-like effect, eliciting pupillary dilatation. This class of agents includes antipsychotropics, antidepressants, the monoamine oxidase (MAO) inhibitors, antihistamines, antiparkinsonian agents, antispasmolytic agents, mydriatic agents, the sympathetic agents, and botulinum toxin.

The pupillary dilatation seen in these cases may be enough to precipitate an attack of angle-closure glaucoma in the patient with narrow angles and to raise

Table 15–4. Nonsteroidal Agents

Antipsychotropic agents
Phenothiazines
Perphenazine (Trilafon), fluphenazine decanoate (Prolixin)
Antidepressants
Tricyclic agents
Amitryptiline (Elavil), imipramine (Tofranil)
Nontricyclic agents
Fluoxetine (Prozac), mianserin HCl (Bolvidin)
Monoamine oxidase (MAO) inhibitors
Phenylzine sulfate (Nardil)
Tranylcypromine sulfate (Parnate)
Antihistamines
Ethanolamines
Orphenadrine citrate (Norgesic)
Antiparkinsonian agents
Trihexyphenidyl HCl (Artane)
Antispasmolytic agents
Propantheline bromide (Pro-Banthine)
Dicyclomine HCl (Bentyl)
Antibiotics
Sulfa, quinine
Sympathomimetic agents
Epinephrine, ephedrine
Phenylephrine
Amphetamine
Hydroxyamphetamine
Mydriatic agents
All agents
Surgical agents
Viscoelastic agents, silicone oil
Botulin toxin
Cardiac agents
Disopyramide phosphate (Norpace)

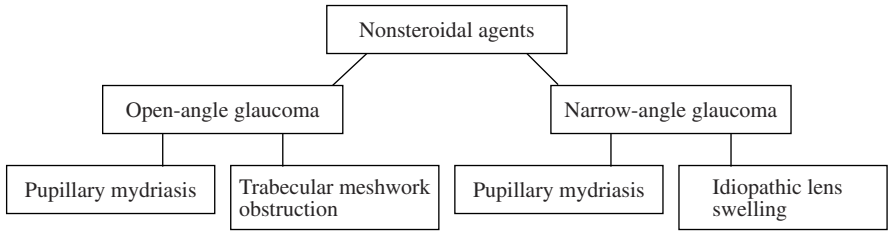

Figure 15–3. Mechanism of action.

the IOP in the patient with open-angle glaucoma. Indeed, Mapstone[56] has shown that when the pupil is in the mid-dilated range of 3 to 5 mm, the eye is at greatest risk for an attack of angle-closure glaucoma. He believes that when the pupil is in this range, the vector forces at work within the eye are greatest for precipitating an attack of angle-closure glaucoma.

With regard to open-angle glaucoma, the causes of the elevated IOP are much more varied, including the release of pigment during the pupillary dilation,[57,58] the subsequent obstruction of the trabecular meshwork,[57,58] and a possible increase of inflow during pupillary dilation.[58]

As an alternative, some agents have been documented to produce an idiopathic swelling of the lens, associated with angle-closure glaucoma. These agents include the antibiotics sulfa and quinine, and aspirin. Some agents directly attack or obstruct the trabecular meshwork, such as the viscoelastic agents and silicone oil. The following sections review the most prominent classes of agents in this diverse group of drugs.

What Is the Role of Psychotropic Agents?

Of the antipsychotropic agents on the market today, only perphenazine (Trilafon)[59] and fluphenazine decanoate[60] (Prolixin) have been documented to have been associated with glaucoma. In both instances these were attacks of angle-closure glaucoma. These episodes were felt to reflect the anticholinergic effect of these agents on the eyes. It was also felt that these patients were at risk for an attack of angle-closure glaucoma.

What Is the Role of Antidepressant Agents, Including the Tricyclics and Nontricyclics?

Amitryptiline[61] (Elavil and Amitril) and imipramine[62] (Tofranil), which are tricyclic agents, have been shown to produce attacks of angle-closure glaucoma. Of the nontricyclic drugs, fluoxetine[63] (Prozac) and mianserin hydrochloride (HCl)[64] (Bolvidon) have been documented to be associated with attacks of angle-closure glaucoma.

What Is the Role of Monoamine Oxidase Inhibitors?

These are antidepressant agents with rather weak anticholinergic action. However, it is felt that their action may accentuate the anticholinergic action of

other agents when combined with them, such as the phenothiazines and the antidepressant agents mentioned above. Specifically, the agents phenelzine sulfate[59] (Nardil) and tranylcypromine sulfate[59] (Parnate) have been shown to be associated with episodes of angle-closure glaucoma.

What Is the Role of Mood-Altering Agents, such as Minor Tranquilizers, Sedatives, and Stimulants?

This is a rather diverse class of agents including sedatives such as diazepam (Valium), morphine, barbiturates, stimulants such as amphetamine, and the methylxanthines such as caffeine and theophylline. Although Valium was reported to have been taken by a patient having an attack of angle-closure glaucoma,[65] this finding was refuted subsequently in the literature,[66] due to the lack of any known effect of Valium upon the eyes. Barbiturates, morphine, paraldehyde, meperidine, reserpine, and phenytoin have not been reported to produce an elevated IOP.

The amphetamines have not been documented in the literature to have produced an elevated IOP in any patient.

The methylxanthines are a rather large and diverse group of agents and can be found in a great variety of agents including the above-mentioned caffeine and theophylline as well as chocolate! Although no reported cases of glaucoma have been reported with these agents, I was recently referred a case of medically uncontrolled open-angle glaucoma. This patient, a 54-year-old black woman on maximal medical therapy, had an IOP of 35 mm Hg in both eyes and optic nerve damage per funduscopy in both eyes. The only remaining positive history was that she was a heavy coffee drinker, by her estimate, having 19 cups of black coffee daily. I immediately prescribed the elimination of all caffeine from her diet, and within 24 hours the IOP was 19 mm Hg in both eyes. On all follow-up visits the patient was caffeine free, and the IOP has been within normal limits—under 21 mmHg. The mechanisms of action to produce an elevated IOP in this case is poorly understood at this time and may be related to the ability of the methylxanthines to block the enzyme phosphodiesterase and to increase intracellular levels of cyclic adenosine monophosphate[67] (cAMP), in contrast to the effect of the β-adrenergic agents such as timolol.[68]

What Is the Role of Antibiotics?

Sulfa Drugs

The sulfa drugs have been well documented to produce an idiosyncratic swelling of the lens associated with shallowing of the anterior chamber, retinal edema, and elevated IOP.[69] These episodes do not involve the pupil and are not responsive to cycloplegic agents, resulting in the present thinking that these cases reflect an idiosyncratic response of the lens to sulfa agents.[70] This observation has been confirmed by A-scan measurements of the eye during such an attack.[71] Some authors feel that the response of the lens to these agents reflects an acute swelling of the ciliary body, resulting in marked zonular relaxation and the subsequent swelling of the lens observed in these cases. This phenomenon

has been observed when sulfa has been used in a variety of agents including antibiotics[69] and antihypertensive agents (e.g., hydrochlorthiazide)[72] and as carbonic anhydrase inhibitors (e.g., acetazolamide).[73]

Quinine

This phenomenon has also been reported to produce an elevated IOP with quinine.[74]

Tetracycline

Tetracycline has also been documented to produce an idiopathic swelling of the lens.[75]

What Is the Role of Antiparkinsonian Agents?

The antiparkinsonian agents act through two mechanisms: (1) replenishing diminished stores of dopamine in the corpus striatum, and (2) acting as a strong anticholinergic. It is those agents in the latter category that we are concerned with. Indeed, trihexyphenidyl HCl[76] (Artane) has been documented to precipitate angle-closure glaucoma. This finding is felt to reflect the anticholinergic action of this agent.[76]

What Is the Role of Antispasmolytic Agents?

These agents act to reduce both the gastric secretion and the motility of the stomach. Their action directly reflects their anticholinergic power. Although no attacks of angle-closure glaucoma have been documented with these agents, propantheline bromide[77] (Pro-Banthine) and dicyclomine HCl[77] (Bentyl) have been documented to raise the IOP in patients with open-angle glaucoma. This effect is felt to reflect their anticholinergic action.

What Is the Role of Anesthetic Agents?

General anesthesia has always entailed increased risk to the patient, including the risk of elevated IOP and glaucoma. It has always been difficult to separate the various risk factors to the patient undergoing general anesthesia. The induction of general anesthesia itself may be associated with an elevated IOP from laryngeal spasm, coughing, and wheezing associated with endotracheal intubation.[78] Although this is a significant risk to the patient with an open globe, what we are most concerned with are those factors introduced by the physician/anesthesiologist at the time of surgery.

Specifically, succinylcholine,[79,80] ketamine,[81] and chloral hydrate[82] have been well documented to raise IOP. This effect is felt to be due to increased extraocular muscle tone from these agents.[83]

The preoperative use of atropine, scopalmine, and ephedrine has been felt to be associated with attacks of angle-closure glaucoma following general anesthesia.[84–86]

Although many factors may be out of the hands of the surgeon and/or anesthesiologist, careful screening of preoperative and intraoperative medications may help to minimize this risk to patients.

What Role Do Surgical Agents Play in Inducing Glaucoma?

Viscoelastic Agents

Hyaluronic acid (Healon) and sodium chondroitin sulfate have been developed to protect the corneal endothelium at the time of intraocular surgery. Both of these agents have been associated with an elevated IOP in the immediate postoperative period.[87,88] This elevated IOP is felt to directly reflect an acute obstruction of the trabecular meshwork outflow channels and is usually seen within 12 to 24 hours after surgery.[89] Although there was some initial feeling that this finding reflected the large molecular weight of these agents, it has also been observed to occur when a low molecular weight substance is used.[90] It is my observation that if these agents are carefully washed out of the eye at the time of surgery, a great deal of these problems will be avoided in the immediate postoperative period.

Silicone Oil

This agent has become popular during pars plana vitrectomy and the repair of complicated retinal detachments. Silicone oil has been associated with attacks of elevated IOP.[91] The silicone oil may emulsify, forming bubbles that may clog the trabecular meshwork.[92] In addition, pupil block glaucoma[93] may also be observed to occur in these patients. This effect is felt to be due to occlusion of the pupil with silicone oil producing iris bombé and acute angle-closure glaucoma.[93] The treatment may vary from a simple washout of the silicone oil from the anterior chamber to a surgical filtering procedures.[94] In the patient at risk for angle-closure glaucoma, an inferior peripheral iridectomy is recommended.[93]

What Role Do Antihistamines Play in Inducing Glaucoma?

The antihistamines are a diverse group of agents that can be broadly broken down into two classes—the H_1 and the H_2 antihistamines. The H_1 antihistamines block the action of histamine on capillary permeability and vascular, bronchial, and other smooth muscles. The H_2 antihistamines also block the effect of histamine on the smooth muscles of the peripheral blood vessels and the secretion of gastric acid. What makes this group of importance is the anticholinergic action of these agents. Although the anticholinergic action is mild, orphenadrine citrate (Norgesic),[95] an H_1 antihistamine, has been documented to have precipitated an attack of angle-closure glaucoma. The H_2 antihistamines cimetidine and ranitidine have been documented to raise the IOP in one patient with glaucoma being treated for a duodenal ulcer.[96] This effect has not

been repeated by other authors. It should also be noted that the H_1 antihistamine promethazine HCl (Phenergan) has been shown to produce an idiopathic swelling of the lens as documented with the sulfa agents.[97] Although the action of these agents on the whole is rather weak, they should be approached with caution in the patient at risk for glaucoma.

What Role Do Autonomic Agents Play in Inducing Glaucoma?

Sympathomimetic Agents

This class of agents has generally been associated with the treatment of glaucoma, through their ability to dilate the pupil, but they may precipitate attacks of angle-closure glaucoma[68,99] and raise the IOP in patients with open-angle glaucoma[98] (Table 15–5). This is important because these agents are found in a wide variety of products including inhalers used for the treatment of asthma and in rectal suppositories.

Parasympatholytic Agents

All of these agents have a marked propensity to dilate the pupil and place the susceptible patient at risk for an attack of angle-closure glaucoma. These agents are found in a wide variety of products from timed-release discs for the treatment of motion sickness (Transderm-Scop)[101] to a variety of inhalers used for the treatment of asthma. These products should be used with caution in the susceptible patient (Table 15–6).

What Role Do Inhalation Agents Play in Inducing Glaucoma?

As mentioned above, a wide variety of agents are found in inhalation products, including the sympathomimetic and parasympathomimetic agents. In addition, salbutamol[102] and ipratropium[103] have also been documented to precipitate attacks of angle-closure glaucoma. This action is felt to be due to the anticholinergic action of ipratropium in combination with the effect of salbutamol on aqueous humor production.[104] These agents should be used with caution in the patient at risk for such an attack of glaucoma.

Table 15–5. Sympathomimetic Agents and Glaucoma

Epinephrine[68*,98+]
Ephedrine[99*]
Phenylephrine[68*,98+]
Hydroxyamphetamine[99*]

*Narrow-angle glaucoma.
+Open-angle glaucoma.

Table 15–6. Parasympatholytic Agents and Glaucoma

Cyclopentolate (Cyclogel)[99,100]
Tropicamide (Mydriacil)[68,100]
Atropine (Atropisol)[68,100]
Homatropine Hydrobromide[68,100]
Scopalomine (Transderm V, Hyoscine)[68,100]

What Role Do Cardiac Agents Play in Inducing Glaucoma?

The traditional cardiac agents including digitalis and quinidine do not appear to have any effect on the IOP. However, interestingly, disopyramide phosphate (Norpace)[105] does appear to have some anticholinergic activity and has indeed been documented to produce an attack of angle-closure glaucoma. Newer agents including the calcium channel blockers have been shown to have mixed results on the IOP at this time.[106,107]

What Is the Role of Botulinum Toxin (Oculinum)?

Botulinum toxin has become popular for the treatment of essential blepharospasm and ocular muscle palsy. This injectable agent has been documented to produce an acute attack of angle-closure glaucoma.[108] The mechanism of action for this is felt to be the effect of this drug on the ciliary ganglion, producing pupillary mydriasis.[109]

What Is the Role of Aspirin (Acetylsalicylic Acid)?

Aspirin has been reported to produce an idiopathic swelling of the lens in association with an elevated IOP.[110] The patient with narrow and/or occludable angles should be cautioned about the use of aspirin.

What Is the Treatment of Nonsteroidal Drug-Induced Glaucoma?

The initial consideration is whether the patient can stop using the offending agent (Fig. 15–4). In many cases, the simple removal of the precipitating agent may be enough to successfully treat the patient. Unfortunately, in many cases, considerable damage may have already occurred, and the patient may need to be treated in the traditional fashion of the patient with glaucoma (Fig. 15–4).

In other patients the offending agent is medically necessary and cannot be stopped without placing the patient at undue risk. In these cases the patient is treated similarly to the patient initially presenting the clinician with traditional glaucoma (see Fig. 15–4). The difficulty in these cases is that with the offending agent still being used, medical therapy is often unsuccessful, requiring more aggressive treatment, including surgery (Fig. 15–4).

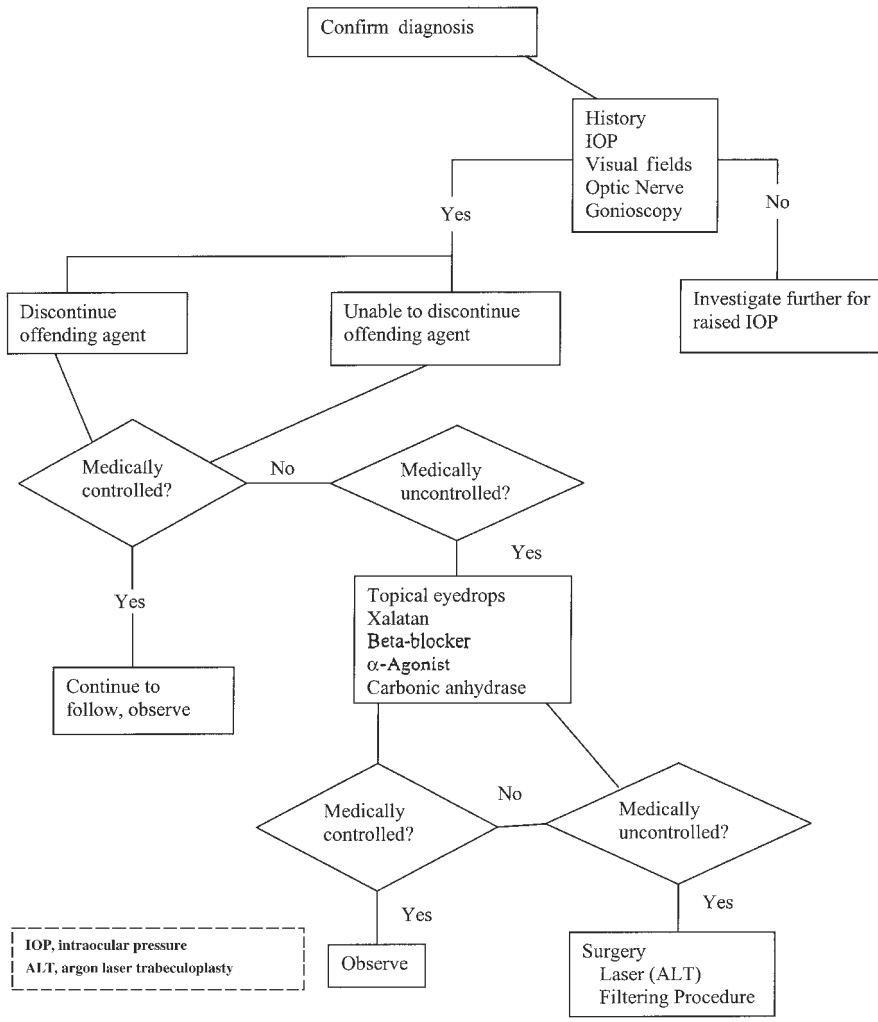

Figure 15–4. Algorithm for management of noncorticosteroid drug-induced glaucoma.

What Is the Key to Successful Treatment?

Overall, the key to successful treatment in all of these patients is time and consideration by the clinician to carefully determine the role that these agents play in the patient's glaucoma.

Future Considerations

What Is New in Drug-Induced Glaucoma?

There is a lot of interest in the question of steroid regulation of trabecular meshwork induced glucocorticoid response protein (TIGR).[111] Topical application of anecortave acetate (AL3789) reduced IOP in glucocorticoid-induced ocular hypertension in rabbits and in humans.[112]

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◆ 16 ◆

Glaucoma Associated with Systemic Disease

Joern B. Soltau

Definition

What Systemic Diseases and Problems Are Associated with Elevated Intraocular Pressure or Glaucoma?

Several groups of systemic diseases can be associated with elevated intraocular pressure (IOP) and/or glaucomatous optic neuropathy: endocrine disorders, vascular disease, collagen vascular disease, renal disease and hemodialysis, hematologic disorders, primary familial amyloidosis, irradiation, systemic viral disease, parasitic disease, dermatologic disorders, and neurologic disorders. For management see Figure 16–1.

GLAUCOMA ASSOCIATED WITH ENDOCRINE DISORDERS

Definition

What Are the Main Endocrine Disorders that Are Associated with Elevated IOP?

Glaucoma occurs in association with several endocrine disorders: pituitary disease, Cushing's syndrome, diabetes mellitus, and thyroid disease. For management see Figure 16–2.

Clinical Pathways in Glaucoma. Edited by Zimmerman and Kooner.
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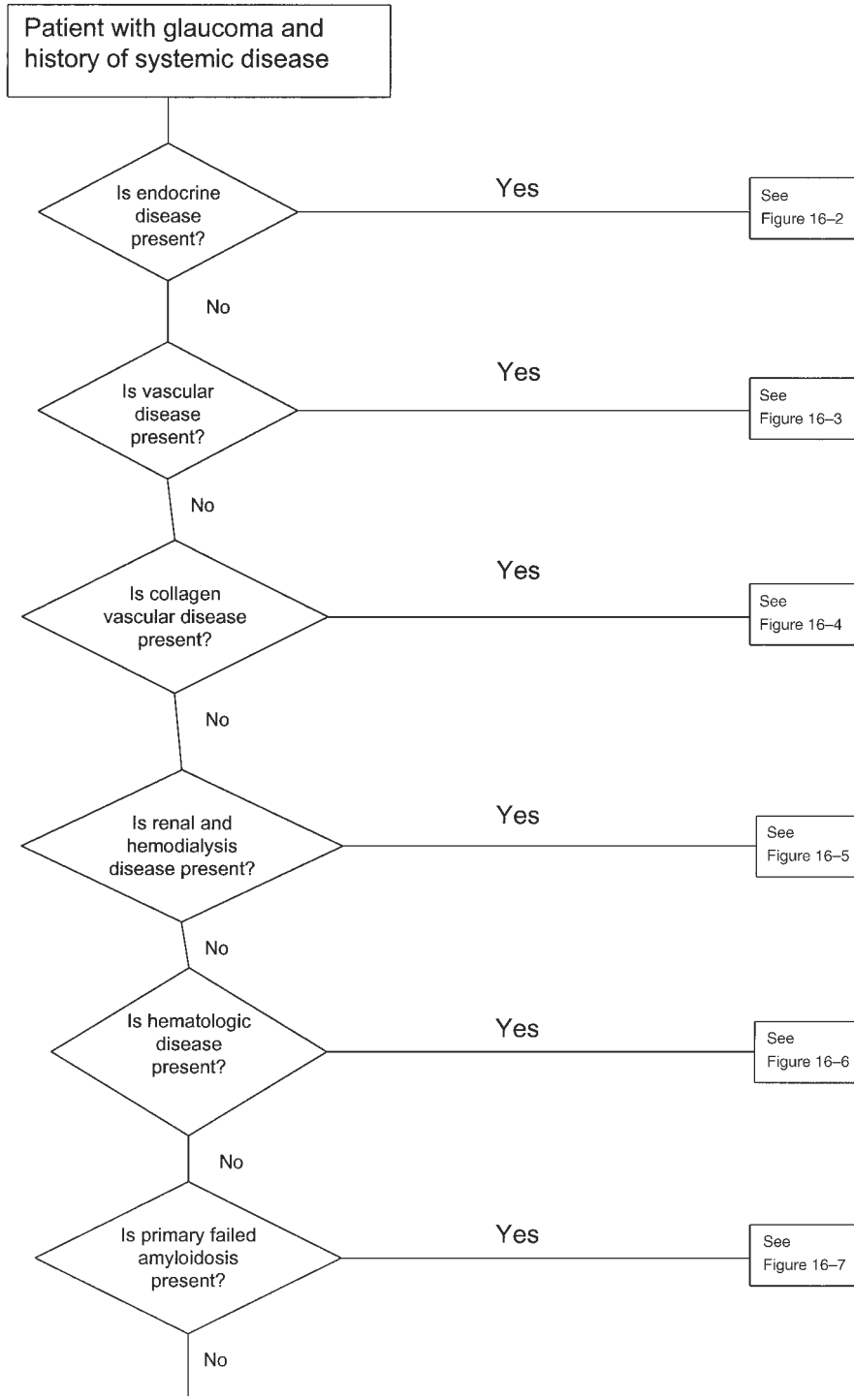

Figure 16-1. Management of a patient with glaucoma and systemic disease(s).

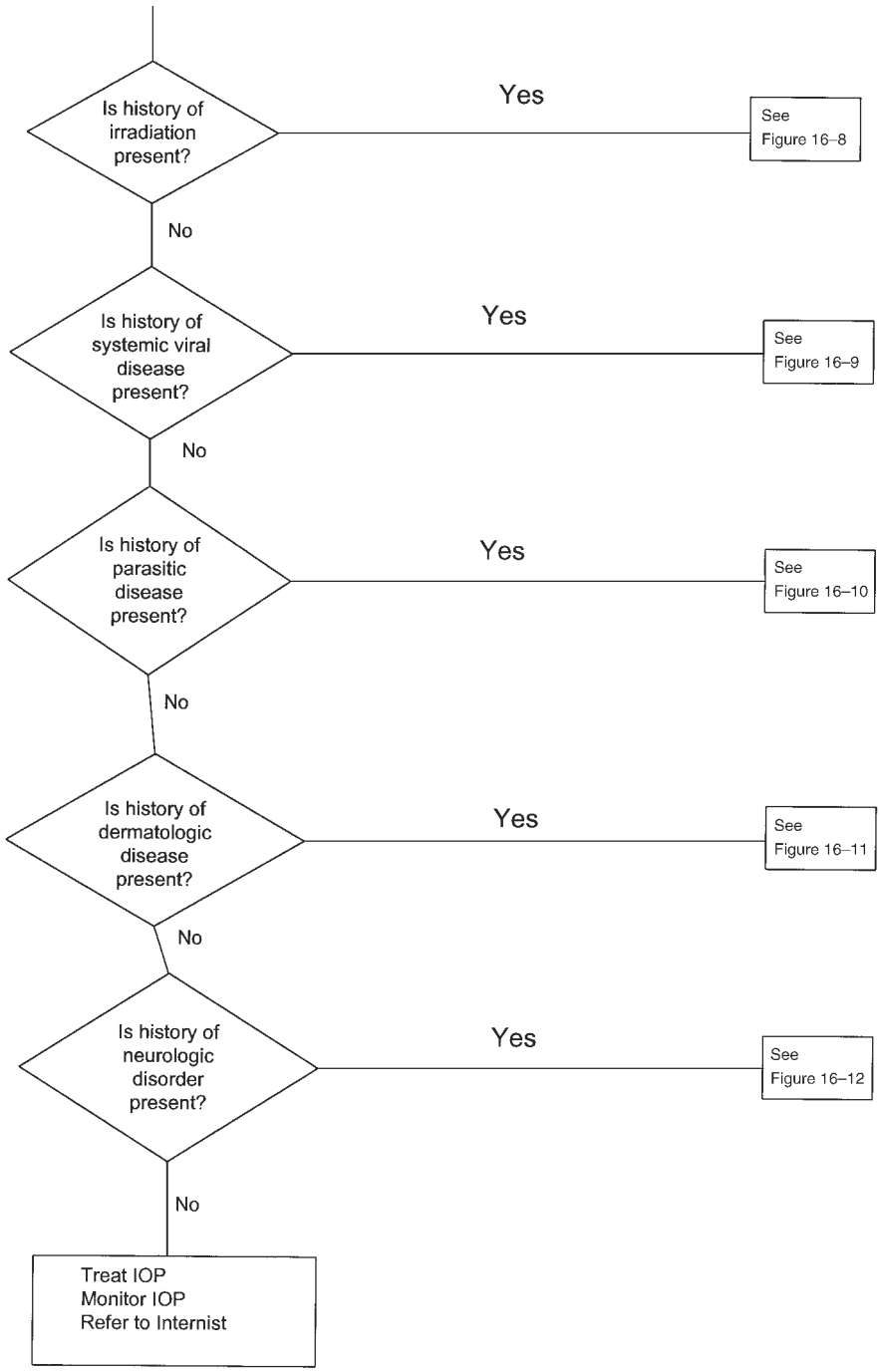

Figure 16-1. *Continued.*

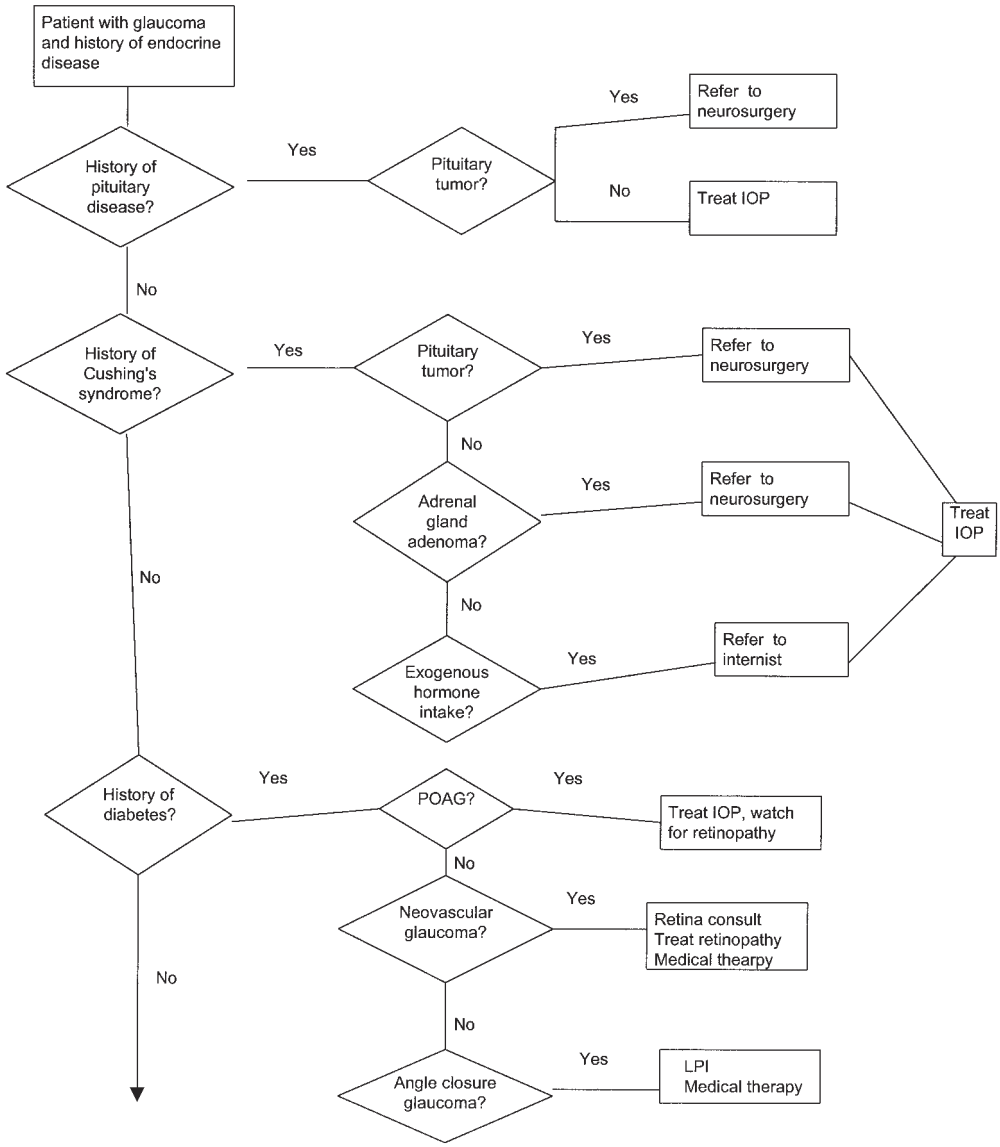

Figure 16-2. Management of a patient with glaucoma and endocrine disease.

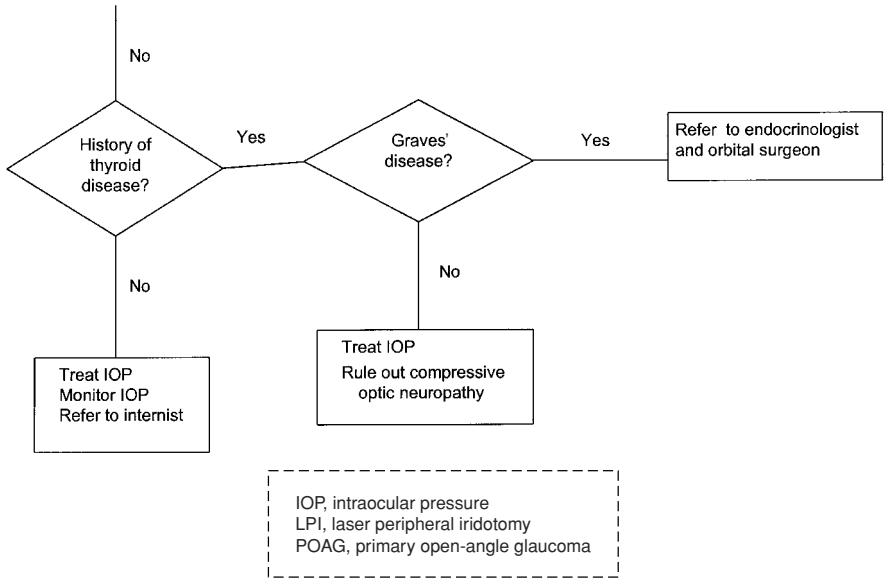

Figure 16-2. ***Continued.***

Glaucoma Associated with Pituitary Disease

Definition

How Does Pituitary Disease Present Clinically?

The two most common types of pituitary adenomas are prolactinomas and somatotropic adenomas. Hyperprolactinemia is the most common form of pituitary hyperfunction. In women hyperprolactinemia causes galactorrhea, amenorrhea, and infertility. In men it causes impotence and diminished libido. Somatotropic adenomas are the second most common form of pituitary adenoma. These tumors produce excess growth hormone, resulting in skeletal growth changes in childhood leading to gigantism. In adults excess growth hormone secretion results in soft tissue swelling and hypertrophy involving the extremities and face, the hallmarks of acromegaly.

Why Is the IOP Elevated in Patients with Pituitary Disease?

There has been a suspicion that IOP can be regulated by neural and/or humoral influences on the rate of aqueous humor formation. However, it is difficult, if not impossible, to separate specific influences of the central nervous system on the IOP from vascular-induced or other secondary alterations. Although there is an association between chronic open-angle glaucoma and pituitary tumors, the exact mechanism by which this occurs is unknown.

Epidemiology and Importance

Is the IOP Elevated in Someone with Pituitary Disease?

In one study, patients with open-angle glaucoma were found to have on average growth hormone levels twice as high as controls after intravenous administration of arginine,[1] and patients with hyperprolactinemia were found to have a sustained increase in IOP after water load compared to normal individuals.[2] However, in a group of patients with acromegaly the elevated IOP was felt to be secondary to a thicker cornea in this group of patients.[3]

Diagnosis and Differential Diagnosis

It is still unclear if there is a direct link between increased growth hormone or prolactin levels and IOP. Therefore, it is paramount to make sure that in patients with the above-named conditions other etiologies for the elevated IOP are excluded and that existing or progressing visual field defects are not caused by the pituitary tumor itself.

Treatment and Management

Treatment of glaucoma in patients with pituitary tumors is the same as that for patients with chronic open-angle glaucoma. Progression in visual field changes may be due to either the glaucoma or the tumor itself. Therefore, special care must be taken when visual field changes are not consistent with optic nerve head changes or are not typical for glaucoma. For example, prominent bitemporal visual field depression should alert the physician to exclude pituitary pathology even in the presence of typical glaucoma related visual field changes.

Future Considerations

Further exploration of the central regulation of IOP may help to understand the pathophysiology of open-angle glaucoma.

Glaucoma Associated with Cushing's Syndrome

Definition

What Is Cushing's Syndrome?

Cushing's syndrome may be associated with corticotropic adenomas of the pituitary gland, adrenal gland adenomas, or exogenous hormone administration. Excessive adrenocorticotropic hormone (ACTH) results in centripetal obesity, hypertension, diabetes, amenorrhea, osteoporosis, and muscle atrophy.

Why Is the IOP Elevated in Patients with Cushing's Syndrome?

The facility of outflow is up to 50% decreased in patients with Cushing's syndrome.[4–6] Excessive ACTH production from a pituitary corticotropic adenoma

causes the adrenal gland to increase secretion of cortisol, which in turn decreases the outflow facility (see Chapter 15).

Is There a Connection Between Chronic Open-Angle Glaucoma and Cushing's Syndrome?

Increased plasma cortisol levels[7–9] and a disturbance of the hypothalamo-hypophyseal-adrenal gland system[10,11] have been found in patients with ocular hypertension and glaucoma.

Epidemiology and Importance

In one study, IOP greater than 21 mm Hg was found in only four eyes of 62 patients with Cushing's syndrome.[12] In another series, 7 out of 29 patients with Cushing's syndrome had IOPs above 23 mm Hg.[13]

Diagnosis and Differential Diagnosis

Cushing's syndrome might be caused by a pituitary adenoma. Therefore, it is of paramount importance to make sure that progression in visual field changes is not caused by compressive optic neuropathy by the tumor itself. Special care must be taken when visual field changes are not consistent with optic nerve head changes or are not typical for glaucoma.

Treatment and Mangement

Glaucoma in patients with Cushing's syndrome is treated the same as chronic open-angle glaucoma. Adrenalectomy with resulting normalization of hormone levels may allow IOP and reduced outflow facility to return to normal.[4–6,12,14]

Future Considerations

Further research into the influence of glucocorticoids on aqueous outflow, on the expression of trabecular meshwork inducible glucocorticoid response (TIGR) protein in particular, will help understand the mechanism of open-angle glaucoma.[15–17]

Glaucoma Associated with Diabetes Mellitus

Definition

Two main types of diabetes exist: type I, insulin-dependent diabetes mellitus, and type II, non–insulin-dependent diabetes mellitus. Chronic open-angle glaucoma, angle-closure glaucoma, and neovascular glaucoma have all been associated with both forms of diabetes mellitus.

Epidemiology and Importance

Is There a Connection Between Chronic Open-Angle Glaucoma and Diabetes Mellitus?

The issue of whether open-angle glaucoma is more prevalent in patients with diabetes mellitus appears to be controversial.[18] Although many studies do show a positive correlation between those two conditions,[6,19–27] other studies do not confirm this association.[28–34] However, some studies have shown that IOP in patients with type I and II diabetes mellitus seems to be higher than in the general population.[23,24,35,36]

Can Diabetes Mellitus Cause an Angle-Closure Attack?

Lens swelling through influx of free water from acute hyperglycemia may precipitate an angle-closure attack in susceptible individuals.[37,38]

Is Neovascular Glaucoma Still an Issue in Diabetic Patients?

Neovascular glaucoma is the final complication of diabetic proliferative retinopathies. Its incidence has significantly decreased due to the improvement of the management of diabetic patients and systematic panretinal photocoagulation.[39]

Diagnosis and Differential Diagnosis

In every patient with diabetes mellitus, the clinician's suspicion needs to be raised to detect ocular complications. For the glaucoma specialist this includes detection of visual field changes that are not secondary to defects caused by retinal photocoagulation for diabetic retinopathy, but rather secondary to glaucomatous optic neuropathy. The evaluation of optic nerve head changes might also be difficult in a patient with active or regressed neovascularization of the disc. Regular gonioscopy is also important to detect early neovascularization of the angle and neovascular glaucoma early in its course.

Treatment and Management

Treatment of glaucoma in association with diabetes mellitus is aimed at the underlying etiology—open-angle glaucoma, angle-closure glaucoma, or neovascular glaucoma. Treating a patient with open-angle glaucoma and diabetes can be very challenging, because visual field changes might be secondary to diabetic retinopathy or laser treatment of the disease. Diabetics with glaucoma seem to have more inferior visual field defects than patients without diabetes.[18]

Future Considerations

It is hoped that future studies will further elucidate the association of diabetes mellitus with open-angle glaucoma. Inhibition of angiogenic factors like vascu-

lar endothelial growth factor (VEGF) that lead to iris and angle neovascularization in diabetic retinopathy will be a new tool to treat neovascular glaucoma.[40]

Glaucoma Associated with Thyroid Disease

Definition

How Does Graves' Disease Present Clinically?

Graves' disease presents with hyperthyroidism with one or more of the triad of diffuse goiter, dermopathy, and ophthalmopathy. Graves' disease usually occurs between the ages of 30 and 50, with women more often affected than men.

How Does Graves' Disease Cause IOP Elevation?

Glaucoma can occur by several mechanisms including elevated episcleral venous pressure through infiltration of the orbital tissues, impaired outflow facility, and fibrosis of the extraocular muscles compressing the globe in the different positions of gaze and thus elevating the IOP.

The association between hypothyroidism and open-angle glaucoma is controversial.[41,42] Systemic thyroid medication did lower IOP in patients with hypothyroidism.[43–46] Thyroid disease might also be a risk factor for normal-tension glaucoma.[47]

Epidemiology and Importance

In one series 24% of patients with thyroid-associated orbitopathy (TAO) were noted to have an IOP greater than 22 mm Hg but less than 30 mm Hg.[48] In another series of 482 patients, 4.8% of patients had open-angle glaucoma or IOP greater than 22 mm Hg.[49] Only a prolonged duration of active TAO in association with ocular hypertension correlated with progression to glaucomatous damage.[48,50]

Diagnosis and Differential Diagnosis

It is important to differentiate visual field and optic nerve head changes in an individual with Graves' disease from changes caused by compressive optic neuropathy related to the infiltrative thyroid orbitopathy.

Treatment and Management

Glaucoma due to thyroid eye disease is treated the same as chronic open-angle glaucoma. In patients with infiltrative ophthalmopathy, high-dose corticosteroids, radiotherapy, extraocular muscle surgery,[49] and orbital decompression[49,51,52] may be indicated for various reasons and may help in the management of the glaucoma.

Future Considerations

Future studies might be able to document a direct influence of thyroid hormone on the regulation of aqueous flow.

GLAUCOMA ASSOCIATED WITH VASCULAR DISEASES

Definition

Ocular ischemia from ophthalmic artery occlusion and internal carotid artery disease, and retinal ischemia from central retinal vein occlusion (CRVO), central retinal artery occlusion (CRAO), branch retinal vein occlusion (BRVO), and cerebrovascular disease, have all been shown to cause glaucoma. For management, see Figure 16–3.

Epidemiology and Importance

Why Are Vascular Occlusive Diseases of the Retina Important?

Ocular ischemia from occlusion of the ophthalmic artery and vascular occlusive disease of the retina can result in the development of rubeosis iridis and neovascular glaucoma. Ischemic CRVO is the most common cause of neovascular glaucoma in this group, with 60% of eyes developing iris neovascularization and 33% of eyes progressing to neovascular glaucoma. Ischemic hemispheric branch retinal vein occlusion (HRVO), nonischemic CRVO, and CRAO are all associated with the development of neovascular glaucoma to a much lesser extent. CRVO has been associated with systemic diseases such as cardiovascular disease, hypertension, and diabetes mellitus, systemic medications such as oral contraceptives and diuretics, and elevated IOP whether on an open-angle or angle-closure basis.[53–59]

Why Are Cerebrovascular Diseases Important?

Neovascular glaucoma may occur secondary to several cerebrovascular diseases such as carotid artery occlusive disease, giant cell arteritis, and Takayasu's disease.[56,60,61] Glaucoma secondary to elevated episcleral venous pressure has been associated with carotid-cavernous sinus fistulas and arteriovenous malformations (see Chapter 6).

Diagnosis and Differential Diagnosis

Screening gonioscopy in eyes with vascular occlusion, especially central retinal vein occlusion, is important to detect angle neovascularization before development of florid neovascular glaucoma.[54,62] Carotid Doppler studies and echocardiogram further diagnose possible causes for ocular ischemia. In patients with symptoms of giant cell arteritis it might be necessary to obtain an erythrocyte sedimentation rate and a temporal artery biopsy.

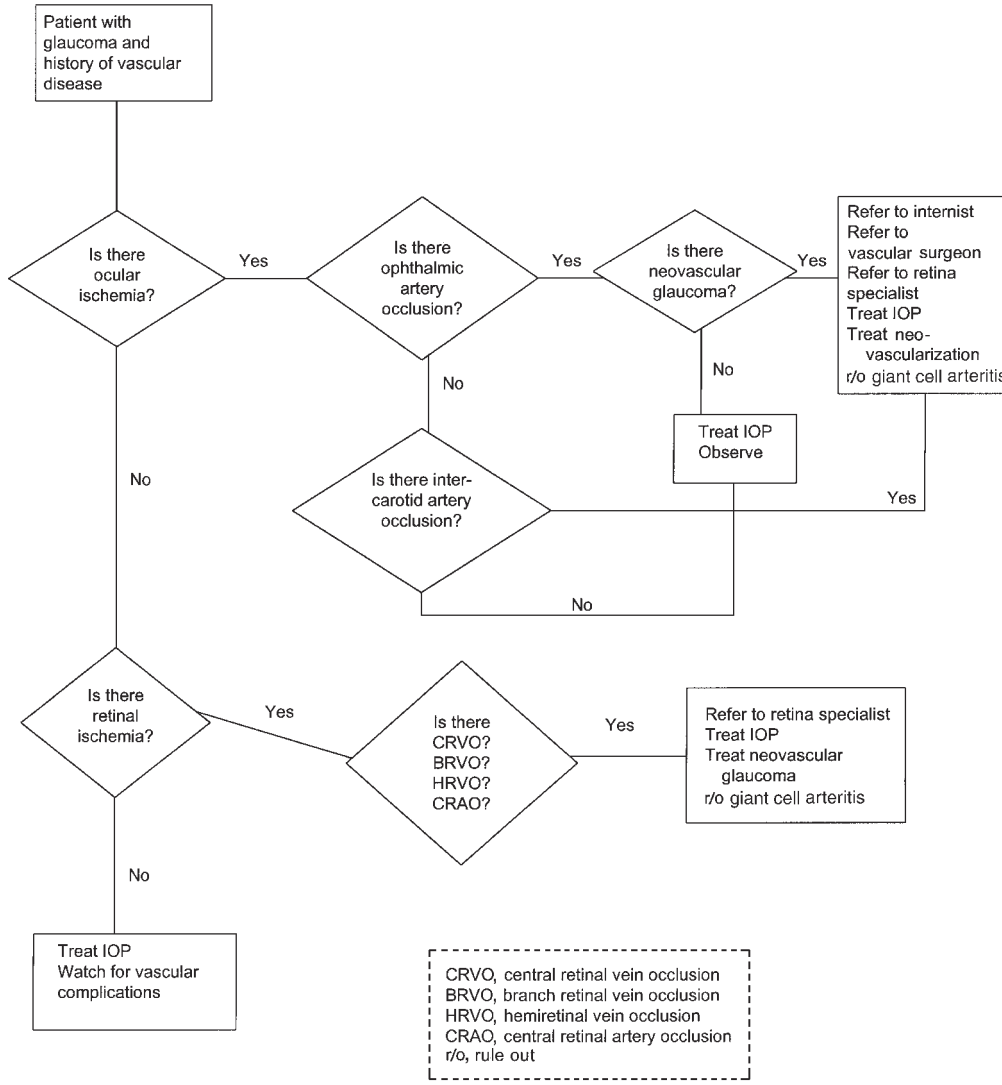

Figure 16-3. Management of a patient with glaucoma and vascular disease.

Treatment and Management

Treatment for glaucoma secondary to vascular occlusive disease of the retina is aimed at the underlying mechanism producing the glaucoma. Neovascular glaucoma is initially treated with cycloplegia, topical steroids, aqueous suppressants, and retinal laser photocoagulation. In patients with open angles and no evidence of neovascular glaucoma, elevated pressure in either eye should be reduced. Angle-closure glaucoma secondary to pupillary block requires an iridotomy. Non–pupillary block angle-closure glaucoma secondary to CRVO can in most cases be treated medically. Implantation of a glaucoma drainage device may be necessary if medical therapy fails to lower the IOP.

Prevention of neovascular glaucoma may be possible with prompt panretinal photocoagulation.[54] Creating a chorioretinal anastomosis, applying recombinant tissue plasminogen activator, cannulating the retinal vein, transecting the posterior scleral ring, and using hemodilution have all been tried in the treatment of CRVO.[63,64]

Treatment of glaucoma secondary to cerebrovascular disease also is aimed at the underlying disease process. Carotid artery occlusive disease may produce neovascular glaucoma. Endarterectomy may be helpful in the management by preventing progressive infarction of ocular tissues. Therapy for glaucoma secondary to elevated episcleral venous pressure such as seen with arteriovenous malformations and carotid cavernous sinus fistulas is for the primary condition, and medical therapy is used to lower the IOP.

GLAUCOMA ASSOCIATED WITH COLLAGEN VASCULAR DISEASES

Definition

Open- or closed-angle glaucoma can occur with keratitis, episcleritis, scleritis, and uveitis in association with several collagen vascular diseases, like juvenile rheumatoid arthritis (JRA), rheumatoid arthritis (RA), scleroderma, Wegener's granulomatosis, systemic lupus erythematosus and relapsing polychondritis. For management, see Figure 16–4.

Epidemiology and Importance

How Often Are Collagen Vascular Diseases Associated with Glaucoma?

Secondary glaucoma due to chronic uveitis can be seen in 14 to 27% of children affected with JRA.[65–69] Four percent of patients with scleritis secondary to rheumatoid arthritis have been found to have glaucoma.[70]

Neovascular glaucoma is a known complication of collagen vascular disease. It has been found in patients with scleroderma,[71] Wegener's granulomatosis,[72] and systemic lupus erythematosus.[73] Relapsing polychondritis has been associated with uveitic glaucoma.[74] Angle closure secondary to uveal effusion and posterior scleritis has been documented in patients with systemic lupus erythematosus.[75,76]

Diagnosis and Differential Diagnosis

It is important to keep in mind that patients presenting with uveitic or neovascular glaucoma can suffer from potentially life-threatening conditions, such as collagen vascular diseases. Appropriate workup and prompt referral to a specialist might be lifesaving.

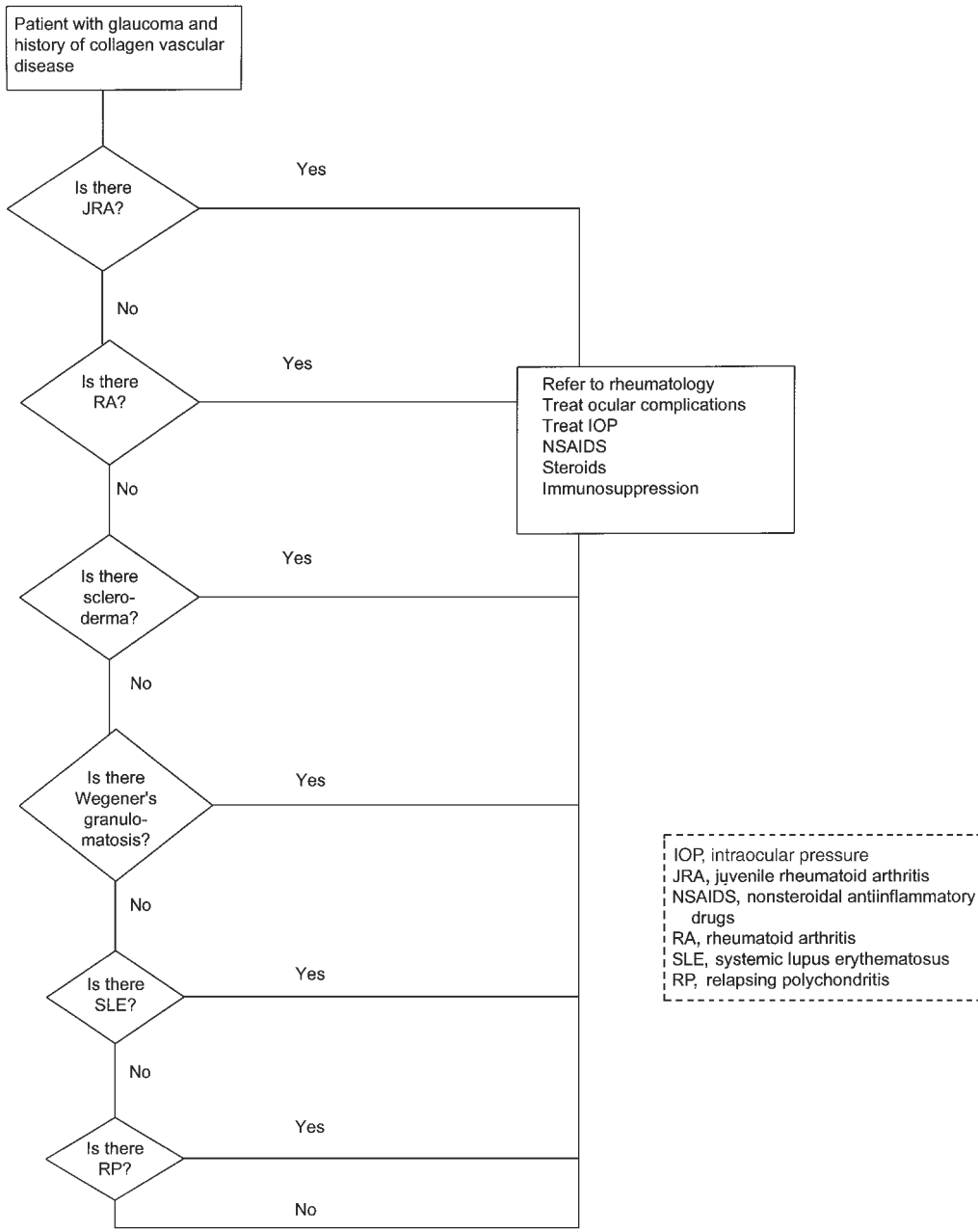

Figure 16-4. Management of a patient with glaucoma and collagen vascular disease.

Treatment and Management

How Is Glaucoma Associated with the Collagen Vascular Diseases Managed?

Treatment is directed at the underlying condition. The mainstay of therapeutics includes nonsteroidal antiinflammatory drugs and oral corticosteroids. Not

infrequently immunosuppressive or cytotoxic agents are necessary to control the disease.

The associated uveitis is treated with topical and/or local corticosteroids and cycloplegics. Occasionally systemic corticosteroids are needed if the inflammation is severe. The secondary glaucoma can be treated medically with aqueous suppressants and occasionally surgically if necessary.

Treatment of neovascular glaucoma is described in Chapter 14.

GLAUCOMA ASSOCIATED WITH RENAL DISEASE AND HEMODIALYSIS

Definition

What Is the Relationship Between Renal Disease and Hemodialysis and Glaucoma?

Elevated IOP can be found in patients during and after hemodialysis,[77] in patients following renal transplantation, and in patients with cystinosis.[78] For management, see Figure 16–5.

Why Is the IOP Elevated in Some Patients During and After Hemodialysis?

During hemodialysis for chronic renal failure, changes in serum osmolality result in fluctuation in IOP. As serum osmolality falls, changes in the osmolality of the intraocular fluids do not occur simultaneously. This results in the flow of free water into the eye raising the IOP. The greater the reduction in outflow facility, the larger the gain in IOP tends to be.[79–81]

However, if an increase of plasma colloid osmotic pressure is induced by removing fluid during hemodialysis, a drop in IOP can be noted.[82,83]

How Is Renal Transplantation Associated with Glaucoma?

Up to one-third of the patients with renal disease requiring transplantation develop elevated IOP postoperatively. This appears to be a steroid response related to the use of systemic steroids to prevent transplant rejection.

By What Mechanism Can Cystinosis Cause Glaucoma?

Cystinosis is a rare metabolic disease characterized by the deposition of cystine crystals in many parts of the body, in particular the kidney and the eye. Cystine crystals have been found in the uvea, conjunctiva, and cornea. A peripheral pigmentary retinopathy can develop in childhood. There has been one report of a young adult with cystinosis who developed an attack of acute angle-closure glaucoma. Pathology specimens of the iris revealed the presence of cystine crystals in the iris stroma and in the iris pigmentary epithelium. Cystine crystals were also found in this patient's conjunctival stroma and conjunctival

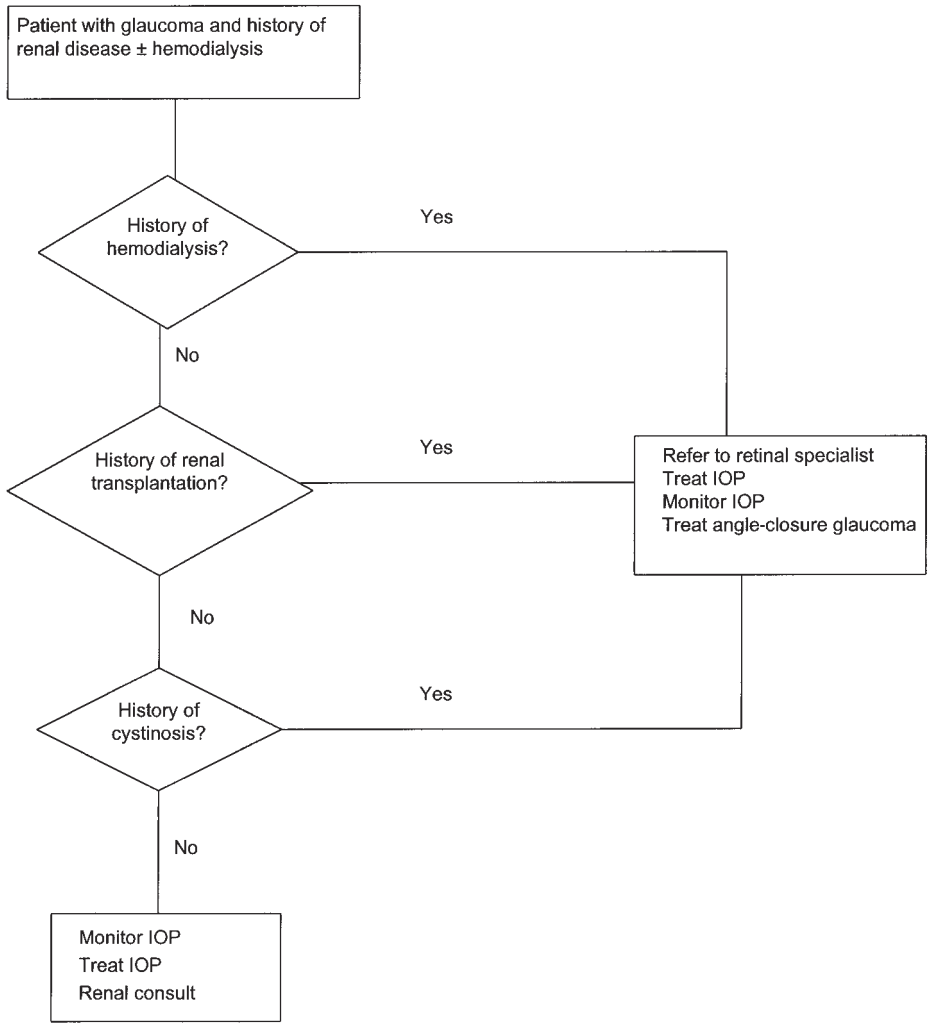

Figure 16-5. Management of patients with glaucoma and renal disease and hemodialysis.

mast cell granules. It was felt that the cystine crystals caused increased iris thickening and rigidity leading to angle closure.[78]

Epidemiology and Importance

Fluctuations of IOP occur during hemodialysis in patients with renal failure. During the first 2 hours of hemodialysis, a small decrease in IOP has been noted, followed by a rise in IOP after prolonged hemodialysis. An average rise in IOP of 7 mm Hg has been noted.[84–86] However, it is not known if these changes are significant enough to cause glaucoma by itself in a nonglaucomatous eye.[77,87–89] With newer hemodialysis techniques a significant change in IOP does not occur.[90,91]

Diagnosis and Differential Diagnosis

In patients with progressive glaucomatous optic neuropathy who are treated with hemodialysis, it might be helpful to monitor the IOP during and shortly after hemodialysis.

Treatment and Management

How Is Glaucoma Associated with Renal Disease and Hemodialysis Managed?

With current hemodialysis techniques, patients without a history of elevated IOP and/or decreased outflow facility are at a very low risk for developing glaucomatous optic neuropathy. On the other hand, eyes with uncontrolled glaucoma and seemingly good IOP control might have IOP spikes during or after hemodialysis. Acetazolamide has been found to prevent pressure spikes in this setting.[92] However, acetazolamide has also been shown to cause severe metabolic acidosis in this setting.[93]

Steroid responders following renal transplantation can be successfully managed with medical therapy. Occasionally they will require glaucoma filtration surgery.

Is Glaucoma a Concern in Patients with Cystinosis?

Because cystinosis is a rare disease, relatively little is known about the treatment of secondary angle-closure glaucoma associated with this disease. Surgical trabeculectomy and iridectomy successfully treated the one case cited in the literature.[78]

GLAUCOMA ASSOCIATED WITH HEMATOLOGIC DISORDERS

Definition

Which Are the Main Hematologic Disorders Associated with Glaucoma?

Glaucoma has been found to be associated with the hyperviscosity syndromes and with the sickle cell hemoglobinopathies. For management, see Figure 16–6.

How Do the Hyperviscosity Syndromes Produce Glaucoma?

The hyperviscosity syndromes refer to a group of diseases that increase serum viscosity and subsequently decrease blood flow. The main clinical entities are polycythemia and the dysproteinemias. The reduction in blood flow results in dilation and tortuosity of the retinal veins. If a secondary central retinal vein

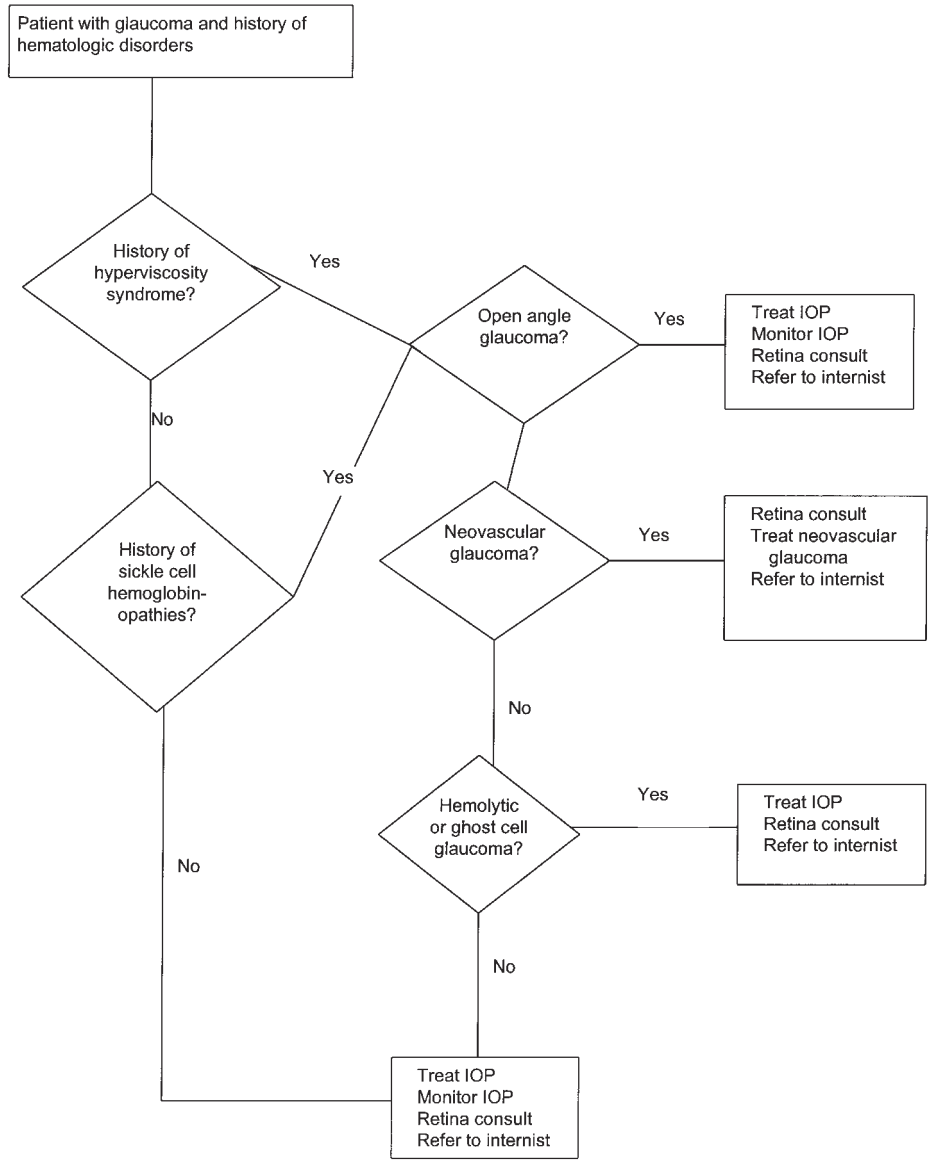

Figure 16-6. Management of a patient with glaucoma and hematologic disorders.

occlusion occurs, neovascular glaucoma can develop.[94,95] A 32-year-old man has been described who developed central retinal vein occlusion with resulting neovascular glaucoma after strenuous activity associated with dehydration.[94]

Does Blood Viscosity Play a Factor in the Etiology of Primary Open-Angle Glaucoma (POAG)?

There are some studies that suggest blood hyperviscosity may play a role in the etiology of POAG.[96,97] However, its role and significance is not fully understood.

By What Mechanisms Can Sickle Cell Hemoglobinopathies Produce Glaucoma?

The sickle cell hemoglobinopathies refer to a group of diseases in which normal adult hemoglobin A is transformed into hemoglobin S, C, or O (Arab) through exchange of a single amino acid in its molecule. The main clinical entities are sickle cell anemia (HbSS), sickle cell trait (HbAS), sickle cell C disease (HbSC), and sickle cell S/O(Arab) disease [HbSO(Arab)]. In sickle cell thalassemia (HbSThal) synthesis of the hemoglobin molecule is impaired.

Under hypoxic conditions the red blood cells in these disorders develop a sickle configuration occluding small blood vessels.[98,99] Both proliferative and nonproliferative sickle cell retinopathy can develop in the peripheral retina mainly in patients with sickle cell C disease and sickle cell thalassemia. Central retinal artery occlusion and central retinal vein occlusion can occur in conjunction with sickle cell anemia. Neovascular glaucoma can develop secondarily in these patients, mainly in patients with HbSC.[100,101] Elevation of IOP might also occur secondary to a blood clot obstructing Schlemm's canal.[102,103] In addition, vitreous hemorrhage secondary to sickle cell retinopathy can cause hemolytic or ghost cell glaucoma.

Introduction of sickle cell erythrocytes into the anterior chamber causes sickling and may result in a large rise of IOP.[104–106] The erythrocytes in the aqueous tend to sickle at a higher rate than in the circulation due to a higher level of ascorbate,[107] or a fall in the pH or P_{O_2} secondary to the hyphema.[108] The sickled red blood cells clog the trabecular meshwork and reduce the facility of outflow.[109]

Patients with the sickle cell hemoglobinopathies are particularly susceptible to central retinal artery occlusion with mild elevation in the IOP[110] or trauma.[111,112]

Epidemiology and Importance

How Often Are the Hyperviscosity Syndromes Associated with Glaucoma?

In one series, 6 out of 15 young patients were diagnosed with blood hyperviscosity associated with central retinal vein occlusion.[95]

How Often Is Sickle Cell Disease Associated with Glaucoma?

Approximately 8 to 10% of African Americans are asymptomatic carriers of one gene for sickle cell disease, and 0.3% carry two genes and therefore have the full-blown disease.[98,99] Individuals with sickle cell disease seem to be more prone to have retinal disease and neovascular glaucoma[100]; however, individuals with sickle cell trait are at a significantly higher risk to develop ocular complications after trauma.[113]

Is Sickle Cell Disease a Risk Factor for Chronic Open-Angle Glaucoma?

Sickle cell disease by itself does not seem to be a risk factor for chronic open-angle glaucoma.[114,115]

Diagnosis and Differential Diagnosis

Every black patient presenting with a traumatic hyphema should be screened for sickle cell disease.[116]

Treatment and Management

How Is Glaucoma Associated with Hyperviscosity Syndromes Treated?

Neovascular glaucoma secondary to the hyperviscosity syndromes is treated with cycloplegics, topical steroids, aqueous suppressants, and retinal laser photocoagulation (see Chapter 14). Open-angle glaucoma secondary to thrombosis in Schlemm's canal can be treated medically with aqueous suppressants.

How Is Neovascular Glaucoma in Patients with Sickle Cell Disease Treated?

Neovascular glaucoma secondary to the sickle cell hemoglobinopathies can be treated medically and with retinal laser photocoagulation. Proliferative sickle cell retinopathy is treated with laser photocoagulation to the involved quadrant; a central retinal artery occlusion or central retinal vein occlusion is treated with panretinal photocoagulation. Filtering surgery or implantation of a drainage device might be necessary (see Chapter 14).

How Is Ghost Cell Glaucoma Treated?

Ghost cell glaucoma secondary to associated vitreous hemorrhage is initially treated medically. However, a vitrectomy might be necessary to remove the cause of the ghost cell glaucoma, a nonresorbing vitreous bleed.

Is Glaucoma Secondary to Trauma Treated Differently in Patients with Sickle Cell Disease?

Certain precautions must be taken when treating elevated IOP secondary to hyphema in sickle cell hemoglobinopathy patients.[116,117] Because mild elevation in IOP can produce irreversible visual loss, aggressive treatment of increased IOP in sickle cell hemoglobinopathy patients must be undertaken. Anterior chamber paracentesis might be warranted.[110,118,119] However, certain medications should be avoided. Acetazolamide can increase the concentration of ascorbic acid in the aqueous, leading to increased sickling of red blood cells in the anterior chamber. Acetazolamide also acts on the kidneys, leading to a metabolic acidosis with secondary increased intravascular sickling and to increased blood viscosity due to its diuretic side effects. It also increases the ascorbic acid levels in the anterior chamber.[107] Methazolamide is much less likely to cause these adverse side effects. Hyperosmolar agents may also increase serum viscosity, leading to vascular compromise in the eye. Epinephrine, apraclonidine, and brimonidine probably should be avoided due to their vasoconstrictive properties reducing anterior chamber oxygenation.[120–122] In

these patients, if the IOP averages greater than 24 mm Hg for any 24-hour period or if there are any spikes in IOP greater than 30, consideration should be given to draining the hyphema by either paracentesis (small hyphemas) or surgically (larger hyphemas).[117,123–126]

Future Considerations

The topical use of aminocaproic acid seems to be promising to prevent complications such as rebleeding in the treatment of patients with traumatic hyphema.[127,128]

GLAUCOMA ASSOCIATED WITH AMYLOIDOSIS

Definition

What Is Amyloidosis?

The term *amyloidosis* describes a group of disorders characterized by extracellular deposition of a substance called amyloid in various tissues. Amyloid consists of delicate protein fibrils that are able to bind Congo red and show green birefringence in polarized light. The relative lack of solubility of these fibrils in physiologic solvents and their resistance to normal digestion is of primary importance. Amyloid deposits may occur in various tissues and organs throughout the body (systemic amyloidosis) or at one specific site (localized or organ-limited).[129,130] For management, see Figure 16–7.

How Does Amyloidosis Cause Glaucoma?

Glaucoma has primarily been associated with primary familial amyloidosis.[129] In this condition, vitreous opacities are the main ocular finding. Amyloid is also found deposited in the eyelids, lacrimal glands, orbit, orbital nerves, extraocular muscles, conjunctiva, cornea, uveal tract, and retinal vessels. Secondary glaucoma may develop due to deposition of amyloid material in the trabecular meshwork.[131–134] Orbital deposition of amyloid causing an increase of episcleral venous pressure has been shown in one case to cause secondary glaucoma.[135]

A high percentage of patients with familial amyloidosis (Finnish type) with lattice corneal dystrophy (Meretoja's syndrome) also have glaucoma.[136] In these eyes amyloid has also been found in the trabecular meshwork, explaining glaucoma in these patients.[137]

Epidemiology and Importance

How Often Is Amyloidosis Associated with an Increased IOP and/or Glaucoma?

In different series, glaucoma has been associated with primary familial amyloidosis in 5%,[138] 6.6%,[139] and four out of 15 cases.[133] In one series of patients with Meretoja's syndrome, glaucoma was found in 23%.[136]

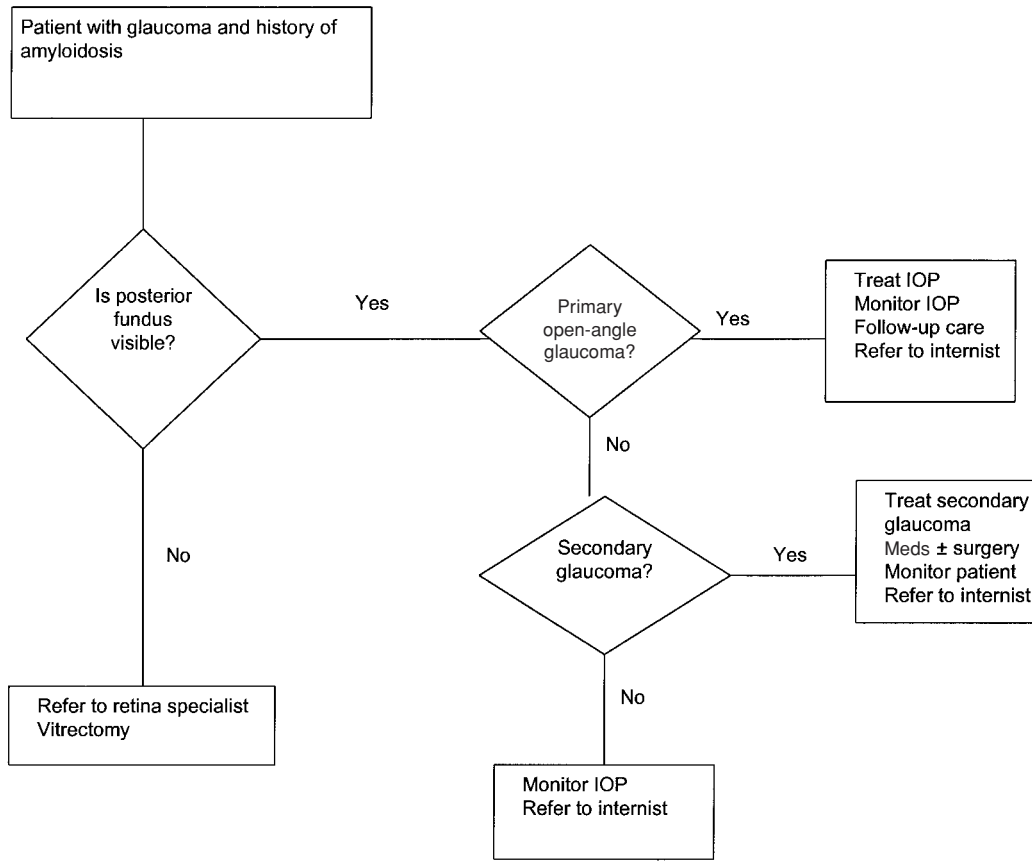

Figure 16-7. Management of a patient with glaucoma and amyloidosis.

Diagnosis and Differential Diagnosis

How Is Glaucoma Associated with Amyloidosis Diagnosed?

Tsukahara and Matsuo[133] examined the eyes of 15 patients with primary familial amyloidosis and found four patients with glaucoma. These glaucomatous patients all had the following in common: (1) systemic symptoms of primary familial amyloidosis, (2) an older age with a longer duration of the disease, (3) vitreous opacities, (4) open angles with pigment deposition in the angles, (5) white flocculent material in the pupillary margin, and (6) a flaky substance on the anterior lens surface, resembling pseudoexfoliation.

Treatment and Management

How Is Glaucoma Associated with Amyloidosis Treated?

Glaucoma secondary to primary familial amyloidosis is treated like open-angle glaucoma with medical therapy followed by surgery for recalcitrant cases.

However, these cases are difficult to follow as the vitreous opacities obscure visualization of the optic nerve head and may hamper interpretation of the visual fields. Vitrectomy can be used to establish the diagnosis and to improve visual function and better visualize the posterior pole. Unfortunately, Doft et al[140] found that 17% of eyes requiring vitrectomy for vitreous amyloidosis were complicated by the development of glaucoma requiring filtration surgery. The conjunctiva might be rather fragile in these eyes, requiring very delicate surgical technique.[134] Epstein[141] noted that survival of filtering blebs may be complicated by the deposition of amyloid within the bleb.

Future Considerations

Amyloidosis is still poorly understood. Further genetic studies will help in the understanding of this group of diseases and gene therapy might be available some day to prevent deposition of amyloid material in organ tissue and thus prevent organ damage such as glaucoma.

GLAUCOMA ASSOCIATED WITH IRRADIATION

Definition

How Is Glaucoma Associated with Irradiation Defined?

Major radiation complications to the eye include radiation cataract, neovascular glaucoma (NVG), retinopathy, and scleral necrosis (in descending order of incidence).[142,143] Radiation to the eye will cause damage to the retinal, choroidal, and iris vascular, resulting in capillary hypoperfusion and eventually neovascularization of the anterior chamber angle.[144] Elevation of the IOP may follow and, with damage of the optic nerve, cause NVG. For management see Figure 16–8.

Epidemiology and Importance

How Often Is Irradiation Associated with an Increased IOP and/or Glaucoma?

The incidence of NVG after irradiation of periocular malignancies is 7%. The onset of symptoms occurred a median of 22 months after irradiation (50 Gy).[145]

In studies that had a follow-up period of less than 6 months, the incidence of glaucoma was less than 2%.[146,147] However, 5 years after plaque radiotherapy of 136 eyes with ciliary body melanomas, 21% of eyes had developed NVG. In this study the development of NVG was significantly related to iris involvement with the ciliary body tumor.[142] Including all uveal melanomas treated with plaque radiotherapy, 15 to 19% of eyes treated with a median apical tumor dose of approximately 100 Gy developed NVG after 5 to 10 years.[148,149] If treated with low-dose radiation (20 Gy) for choroidal hemangiomas, one out of 51 eyes developed NVG.[150]

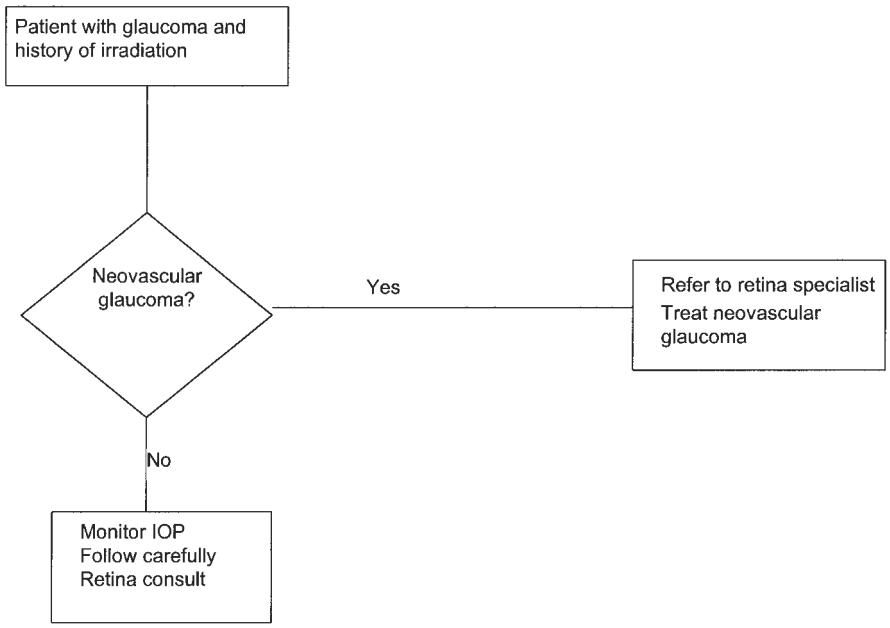

Figure 16-8. Management of a patient with glaucoma and history of irradiation.

Diagnosis and Differential Diagnosis

How Is Glaucoma Associated with Irradiation Diagnosed?

Because neovascular glaucoma can occur months to years after irradiation of the eye, regular careful examination of the iris and anterior chamber angle for neovascularization is of paramount importance. The differential diagnosis includes all other causes of neovascular glaucoma (see Chapter 14).

Treatment and Management

How Is Neovascular Glaucoma Associated with Irradiation Treated?

The treatment of neovascular glaucoma is described in Chapter 14.

Future Considerations

Early detection of intraocular tumors and advanced radiation techniques with concentration of treatment inside the tumor will be beneficial in decreasing long-term ocular complications.

GLAUCOMA ASSOCIATED WITH SYSTEMIC VIRAL DISEASE

Definition

How Is Glaucoma Associated with Viral Diseases Defined?

Viral ocular infections are a significant source of patient morbidity throughout the world. No part of the eye is immune to viral invasion. Viral infections can give rise to keratitis, scleritis, and/or uveitis, which then can lead to decreased aqueous outflow and thus elevated IOP and glaucoma. For management, see Figure 16–9.

HERPESVIRUS

Herpesviruses are DNA viruses. They can infect a variety of animals, including humans. More than 50 different viruses are known; however, only five of this group can cause ocular disease in humans. These are herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV).[151] Secondary to the viral infection a keratitis, scleritis, and/or uveitis may occur, which can give rise to an elevated IOP and thus glaucoma.

Herpes Simplex Virus Herpes simplex virus (HSV) infection may present as superficial keratitis, disciform keratitis, necrotic stromal keratitis, neurotrophic ulcer, and retinitis. Increased IOP in ocular herpes infection associated with uveitis varies from 28 to 40%, but only 10% have secondary glaucoma.[152,153] Disciform and necrotic stromal keratitis is more commonly associated with increased IOP. In severe cases the incidence can reach 80%.[152] Obstruction of the trabecular meshwork with inflammatory products, trabeculitis,[152,154] and acute[155] and chronic[156] angle closure are the most common cause for IOP elevation in herpetic uveitis. Most recently, HSV has been identified in the trabecular meshwork of a patient with keratitis and glaucoma requiring filtering surgery.[157]

The initial management of elevated IOP is directed at controlling viral replication. Oral and/or topical acyclovir and topical trifluridine are most effective because they penetrate the ocular tissues easily. Topical cycloplegics are helpful to control ciliary spasm, and topical corticosteroids may be used if inflammation is severe or persists despite the antiviral treatment. Topical steroids alone can reactivate or aggravate the herpetic infection. They therefore should never be used without initial antiviral coverage. IOP usually returns to normal levels when the inflammation subsides. Aqueous suppressants are effective if IOP needs to be controlled. About 10% of patients who have persistent IOP elevation despite medical treatment may require surgery.[152]

Varicella-Zoster Virus VZV is the etiologic agent of the most common primary infectious childhood disease, varicella or chickenpox. In its recurrent form it may cause herpes zoster or shingles, as it reactivates from the latent stage established during primary illness. Ninety percent of the population in the United States are seroconverted by age 60. When VZV reactivates from its

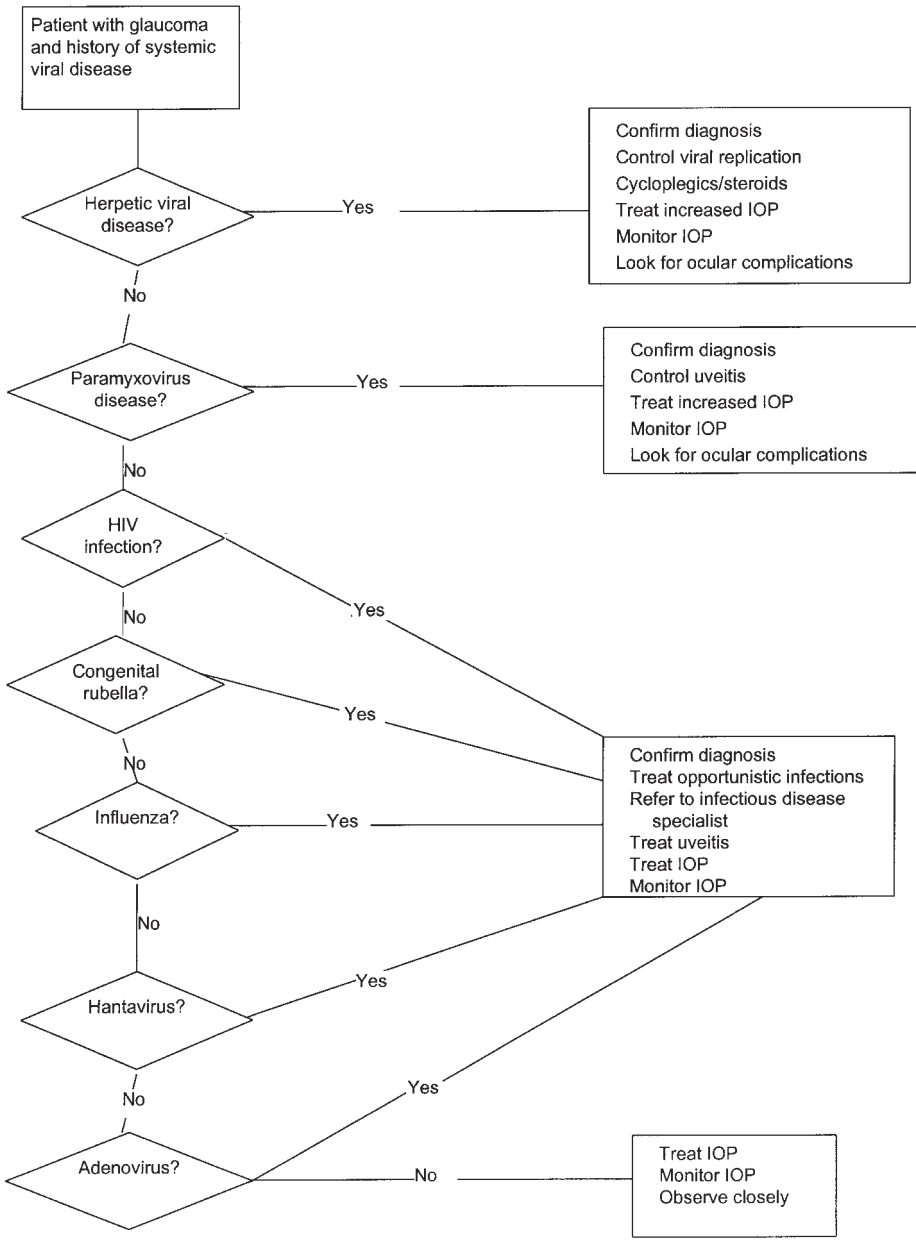

Figure 16-9. Management of a patient with glaucoma and systemic viral disease.

latent form involving the first branch of the trigeminal nerve, it is referred to as herpes zoster ophthalmicus (HZO).[158] VZV reactivates as zoster in one out of five people during the course of a lifetime. Skin lesions involving the side or the tip of the nose suggest ocular involvement because of involvement of the nasal branch of the nasociliary nerve (Hutchinson's sign). HZO is rare in children; it tends to be short-lived, not as painful as in adults, and leaves little to no scarring. In some cases it may be the initial presentation of AIDS; any young

person presenting with HZO should be tested for human immunodeficiency virus (HIV) infection.

Ocular involvement occurs in two-thirds of patients with HZO. This might include conjunctivitis, superficial keratitis, stromal keratitis, neurotrophic keratitis, uveitis, scleritis, retinitis, choroiditis, and optic neuritis. Elevation of IOP and glaucoma occurs in 16 to 50% of cases if the keratitis and uveitis is associated with corneal involvement.[159–161] Decreased outflow facility due to trabeculitis and inflammatory debris in the trabecular meshwork is thought to cause the IOP elevation.[162,163] Oral acyclovir given early in the course of the disease seems to reduce the risk of complications, such as uveitis and associated elevated IOP.[164] Later in the course of the disease uveitis is no longer due to viral replication, but rather to ischemia.[165]

Uveitis and IOP should then be treated with topical corticosteroids, mydriatics, and aqueous suppressants as indicated.

Cytomegalovirus Infection with cytomegalovirus (CMV) is very common among the general population, but in most cases the disease is not clinically apparent. In immunocompromised patients and neonates, it is the cause of significant morbidity and mortality. In older children and young adults, CMV can cause a syndrome resembling infectious mononucleosis and can be associated with a nonspecific follicular conjunctivitis. Infection in patients with AIDS will present as a retinitis. It is the most common ocular infection in patients with AIDS in the United States.[166]

Epstein-Barr Virus Epstein-Barr virus (EBV) is the most common cause of infectious mononucleosis with the classic triad of fever, sore throat, and lymphadenopathy. Seropositivity in the general population is over 90% and transmission occurs primarily through saliva, but also through blood transfusions. It can cause oculoglandular syndrome, follicular conjunctivitis, keratitis, uveitis, retinitis, and papillitis. Treatment consists of oral acyclovir.[167,168] IOP elevation may occur, but glaucoma has not been documented.

Paramyxovirus

Measles Measles causes an acute infection characterized by fever, cough, coryza, and conjunctivitis. Ocular findings are initially limited to the conjunctiva. During this prodromal phase, virus is spread throughout the reticuloendothelial system and within the subepithelial conjunctival lymphoid tissue, resulting in conjunctivitis. A watery-mucoid discharge is usually present. The conjunctivitis is self-limiting and usually resolves as fever defervesces.

Measles can affect the cornea, resulting in a superficial punctate keratitis, initially involving the limbus with later spread to the central cornea. Lesions of the cornea appear to peak after the appearance of the measles rash. Postmeasles blindness (PMB) is a significant complication of measles, as a result of optic neuritis, chorioretinitis, or complications of corneal origin. In Africa 14 to 33% of childhood blindness is due to measles.[169] Complicating this is the increased susceptibility of PMB in patients with vitamin A deficiency, concomitant herpes simplex infection, and/or the use of folk remedies.[169,170] Ocular therapy is mainly supportive, unless bacterial superinfection is evident. Vitamin A supplementation may be useful in those deemed deficient.

Mumps The most common ocular findings in mumps is inflammation of the lacrimal gland. The gland may be tender with chemosis and lid edema. Involvement is usually bilateral and nonsuppurative. Follicular conjunctivitis, keratitis, and anterior uveitis have been described and usually occur during convalescence. Symptoms may include photophobia, tearing, and painless loss of vision. Acute ocular hypotony as well as transient IOP elevation associated with keratitis and anterior uveitis have both been documented with mumps. A painful red eye is typical with decreased visual acuity. Topical corticosteroids and cycloplegics relieve the uveitis in 1 to 4 weeks.

Human Immunodeficiency Virus (HIV)

Ocular manifestations of HIV infection include noninfectious microangiopathy (HIV retinopathy), opportunistic ocular infections, ocular adnexal neoplastic involvement, and neuro-ophthalmic lesions. Opportunistic ocular infections such as CMV retinitis, VZV retinitis, fungal retinitis, and pneumocystosis can all cause secondary uveitis and lead to IOP elevation and thus glaucoma. Bilateral angle closure has been associated with HIV infection.[171–176] Choroidal effusion with secondary anterior rotation of the ciliary body at the scleral spur could be diagnosed with ultrasound biomicroscopy.[171,173] Treatment consists of application of aqueous suppressants, cycloplegics, and topical steroids.

Congenital Rubella

The last rubella epidemic in the United States occurred in 1964. An estimated 10% of pregnant women were exposed to the virus; 2% of women developed clinical rubella, 40% of those in the first trimester. Approximately 10% of mothers with clinical rubella had children with the congenital rubella syndrome.[177] In the U.S., at least 10,000 infants were born with moderate to severe manifestations during that epidemic.[178] In a 20-year follow-up study, ocular disease was noted in 78% of patients, sensorineural hearing loss in 66%, psychomotor retardation in 62%, cardiac abnormalities in 58%, and mental retardation in 42%.[179] Ocular consequences of the congenital rubella syndrome are not limited to abnormalities noted in the neonatal period. Additional abnormalities may appear years and even decades after birth. In a series of 34 rubella patients, 29 (85%) of patients had a cataract, in 21 of these they were bilateral. Microphthalmia was present in 28 of these of infants (82%), and it was bilateral in 22. Glaucoma occurred in 32% (11 cases). In 11 eyes of six of these patients, glaucoma occurred months to years after cataract surgery.[180] In a series of 13 patients, glaucoma was diagnosed 3 to 22 years after birth. The eyes involved were microphthalmic in all but two cases. In all cases the lens had been removed early in life due to cataract.[181]

Congenital rubella syndrome, especially when associated with microphthalmia, was found to be a risk factor for development of glaucoma after cataract surgery in childhood.[179,182]

Influenza

Influenza is an acute febrile illness characterized by malaise, headache, and myalgias. The illness lasts 2 to 7 days. Recovery is complete unless secondary bacterial infections occur. Influenza can be serious and may cause cardiopul-

monary complications or death in elderly or debilitated patients. Ocular involvement with influenza includes conjunctivitis, a mild iritis, interstitial keratitis, dacryoadenitis, and retinitis.[183] Primary angle-closure glaucoma has been reported in three cases.[184]

Hantavirus Infections

Viruses of the *Hantavirus* genus (HTV) chronically infect rodents without apparent disease, but when they are spread by aerosolized excreta to humans, two major clinical syndromes result: hemorrhagic fever with renal syndrome (HFRS) and *Hantavirus* pulmonary syndrome (HPS). Both diseases appear to be immunopathologic, and inflammatory mediators are important causing clinical manifestations. In HPS, T cells act on heavily infected pulmonary endothelium, and it is suspected that γ-interferon and tumor necrosis factor are major agents of a reversible increase in vascular permeability that leads to severe, noncardiogenic pulmonary edema. HFRS has prominent systemic manifestations. The retroperitoneum is a major site of vascular leak, and the kidneys suffer tubular necrosis. Both syndromes are accompanied by myocardial depression and hypotension or shock. HFRS is primarily a Eurasian disease and is caused by the Puumala, Hantaan, and Seoul viruses, whereas HPS appears to be confined to the Americas. The Sin Nombre and New York–1 viruses have been implicated as the etiologic agent.[185,186] Ophthalmic symptoms have been reported with Puumala virus infections in 82% of patients with HFRS; 41% reported photophobia and 50% impaired vision.[187] In another study, frontal headache or periocular pain was noted in 76%, blurred vision in 54%, and photophobia in 11% of patients; 41% were noted to have a myopic shift, and 14% had signs of anterior uveitis. A decrease of the IOP was found in 66% of patients.[188] One patient was described to have a myopic shift secondary to thickening of the lens and forward displacement of the iris-lens diaphragm, and low IOP probably secondary to electrolyte imbalance.[189] Angle-closure attack has also been reported.[190,191]

Adenovirus

Adenovirus can produce a wide range of ocular infections, ranging from follicular conjunctivitis to severe keratoconjunctivitis with corneal opacities. Adenovirus 8 and 19 are commonly implicated with epidemic keratoconjunctivitis and types 3, 4, 7, and 14 with pharyngoconjunctival fever. The risk of visual impairment is greater with the epidemic form of keratoconjunctivitis. Elevated IOP has been described with adenovirus type 10 keratoconjunctivitis.[192]

Future Considerations

Advances in antiviral therapy will make it possible to better treat ocular viral infections and thus prevent a complication such as glaucoma. Multiple agents for the treatment and prevention of viral illnesses have been developed during the past few years. This has been to a great extent in direct response to the HIV virus type 1 epidemic.[193,194] In addition, gene therapy might soon be available to treat viral diseases.[195]

GLAUCOMA ASSOCIATED WITH PARASITIC DISEASE

Definition

What Parasitic Diseases Can Cause Glaucoma?

Parasitic infections of the eye can be caused by protozoans and by helminthes. In response to the ocular infection, a keratitis, scleritis, or uveitis can occur, which subsequently can cause the IOP to rise and eventually can lead to uveitic glaucoma. Among the protozoans *Toxoplasma gondii*, ameba (*Acanthamoeba*), *Leishmania*, and *Plasmodium* have been shown to cause elevated IOP and /or glaucoma. Among the helminthic diseases *Onchocerca, Toxocara, Cysticercus, Echinococcus, Loa loa, Schistosoma, Trichinella*, and others have been shown to cause ocular infections that may lead to glaucoma. For management, see Figure 16–10.

Glaucoma Caused by Protozoan Diseases

Definition

What Is Toxoplasmosis and How Does It Affect the Eye?

Toxoplasmosis is an infectious disease characterized by fever, weight loss, and lymphadenopathy. It is caused by *T. gondii*, which is an obligate intracellular

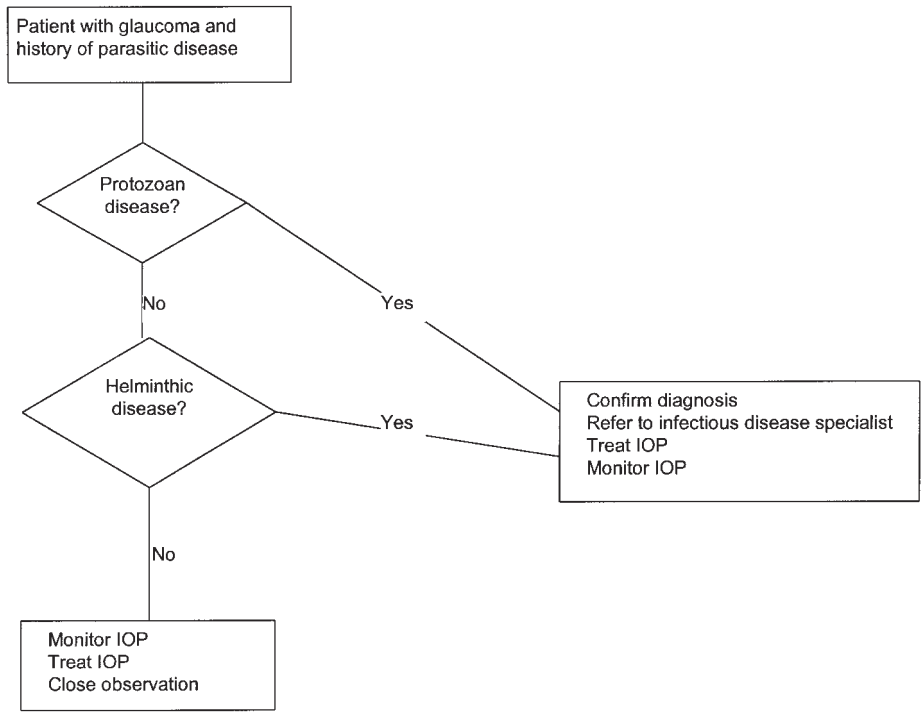

Figure 16-10. Management of a patient with glaucoma and parasitic disease.

protozoan found in most parts of the world. The cat or its close feline relatives appear to be the definite hosts. The oocysts, which are excreted in cat feces, are highly resistant and may remain infective for more than 1 year. Usually only young cats are infective for a short period of time. The infected cat is not the primary source of infection for humans, but it is a very important cause of contamination of the environment.[196] Ocular toxoplasmosis is usually considered a recurrence of a congenital infection, but can also be acquired postnatally.[197,198] In the eye, the retinal tissue and adjacent choroid are the site of infection. The typical ocular lesion is a localized necrotizing retinitis or satellite lesion of an existing scar. Cells are present in the overlying vitreous causing the characteristic appearance of a "headlight in the fog."

What Is Acanthamoebiasis and How Does It Affect the Eye?

Acanthamoeba species are an important cause of microbial keratitis that may cause severe ocular inflammation and visual loss. Like other protozoa, *Acanthamoeba* are unicellular and can exist in two forms: active trophozoite and dormant cyst. The trophozoite is motile, proliferates, and feeds on bacteria, fungi, and other unicellular organisms and cells, like corneal epithelium.[199]

What Is Leishmaniasis and How Does It Affect the Eye?

Leishmania protozoa are obligate intracellular parasites and are transmitted by bites of infected sand flies. Leishmaniasis presents as either cutaneous or visceral (kala-azar or dumdum fever) leishmaniasis depending on the *Leishmania* species and immune status of the patient. In ocular disease, the adnexae are most commonly involved,[200] but anterior uveitis with elevated IOP and glaucoma have been reported.[201–204]

What Is Malaria and How Does It Affect the Eye?

Malaria is caused by infection with the protozoans *Plasmodium falciparum*, vivax, malariae, and ovale. It is transmitted through a bite by the female mosquito of the genus *Anopheles*. Malaria is characterized by fever with sweats, myalgia, headaches, malaise, and sometimes rigors.

Ocular complications occur especially with cerebral malaria. They include retinal hemorrhages, disc swelling, and retinal edema.[205]

What Is Trypanosomiasis and How Does It Affect the Eye?

African trypanosomiasis (African sleeping sickness) is caused by *Trypanosoma brucei* and transmitted by bites of the tsetse fly. American trypanosomiasis (Chagas' disease) is caused by *Trypanosoma cruzi* or wrangle. Chagas' disease has multiple modes of transmission: vector-borne (reduviid bugs) by contamination of the bite wound with vector feces, congenital, and transfusional.[206] Intraocular involvement is rare and may consist of retinal pigment epithelial changes.[207]

Epidemiology and Importance

How Common Is Toxoplasmosis?

Toxoplasmosis is the most common cause of posterior uveitis. In the U.S. approximately 3,000 infants are infected annually.[208] In an adult population the annual incidence for ocular involvement is approximately 0.3 per 100,000 population,[209] and 3% of patients with acquired toxoplasmosis have ocular disease.[210]

How Common Is Glaucoma in Toxoplasmosis?

Transient open-angle glaucoma occurs in about 13% of patients.[211]

How Common Is Acanthamoeba Keratitis?

Acanthamoeba is a ubiquitous, free-living protozoan that is found in all types of liquid media, including tap water, swimming pools, hot tubs, and contaminated contact lens solution. The organism's prevalence seems to peak during warmer weather. The first cases of *Acanthamoeba* keratitis were recognized in 1975, but the disease remained very rare until the 1980s, when an increase in incidence mainly associated with contact lens wear was reported.[199]

How Common Is Glaucoma in Acanthamoeba Keratitis?

Secondary uveitic glaucoma has been reported but is rarely a problem.[212,213]

How Common Is Leishmaniasis?

Leishmaniasis is a worldwide disease. Kala-azar (visceral leishmaniasis) has reemerged from near eradication. The annual estimate incidence and prevalence of kala-azar cases worldwide is 0.5 million and 2.5 million, respectively. Of these, 90% of the confirmed cases occur in India, Nepal, Bangladesh, and Sudan.[214]

How Common Is Glaucoma in Leishmaniasis?

Intraocular involvement in leishmaniasis is rare, but probably underdiagnosed.

How Common Is Malaria?

Malaria is the most important infectious disease in the world with 300–500 million cases and approximately 2 million deaths per year.[215]

How Common Is Glaucoma in Malaria?

Glaucoma is a rare complication of malaria. There are only two reports in the literature about glaucoma secondary to malaria.[216,217]

How Common Is Trypanosomiasis?

In Africa 60 million people are at risk of infection with human African trypanosomiasis or sleeping sickness, with about 300,000 new cases each year. However, only 10% of cases are probably diagnosed and treated.[218] In Central and South America, Chagas' disease is of great epidemiologic importance; 100 million persons are at risk of infection, approximately 18 million are infected, and 50,000 deaths annually can be attributed to the disease.[219] The reservoir for the protozoa *T. cruzi* involves over 175 species.[206]

How Common Is Glaucoma in Trypanosomiasis?

Glaucoma has not been reported, but a marked postural drop of the IOP has been noted, possibly secondary to changes in the autonomic innervation secondary to the parasitic infection.[220]

Diagnosis and Differential Diagnosis

How Is Toxoplasmosis Diagnosed?

Classic ocular toxoplasmosis is diagnosed clinically. The typical ocular lesion is a localized necrotizing retinitis or satellite lesion of an existing chorioretinal scar. Cells are present in the overlying vitreous causing the characteristic appearance of a "headlight in the fog." The anterior segment of the eye may also be involved in the inflammatory process. An anterior uveitis, which can be either granulomatous or nongranulomatous in character, can be seen only in an eye with an active toxoplasmosis lesion of the retina. Therefore, all patients presenting with an anterior uveitis should have a dilated examination of the retina to rule out an underlying disorder of the posterior segment.[221]

Laboratory tests can be used to help confirm the clinical diagnosis. More and more, polymerase chain reaction techniques are replacing the Sabin-Feldman test, which uses live *Toxoplasma* organisms, complement fixation, and enzyme-linked immunosorbent assays.[222]

What Are the Ocular Complications of Toxoplasmosis?

Complications of ocular toxoplasmosis occur in approximately one-third of patients and include chronic iridocyclitis, cataracts, band keratopathy, cystoid macular edema, retinal detachment, and optic atrophy. Transient open-angle glaucoma occurs in about 13% of patients.[211] An interesting association with Fuchs' heterochromic iridocyclitis has been reported; however, its causal relationship is unproven and controversial.[223–225]

How Does Acanthamoeba Keratitis Present and How Is It Diagnosed?

The clinical picture is often characterized by severe pain with an early superficial keratitis that is often treated as herpes simplex infection. Subsequently,

a characteristic radial perineural infiltration may be seen, and ring infiltration is common. Limbitis and scleritis are frequent.[226] Laboratory diagnosis is primarily by culture of epithelial samples inoculated onto agar plates spread with bacteria. Recently, *Hartmannella* has also been shown to cause amebic keratitis.[227]

How Is Leishmaniasis Diagnosed?

In endemic areas the diagnosis is made on clinical grounds. A definite diagnosis of leishmaniasis is made by documenting the parasite in smears of bone marrow, splenic aspirates, or in biopsies from cutaneous lesions.[228] Ocular leishmaniasis is diagnosed by the temporal relationship to the systemic manifestation. However, the parasite has also been isolated from the anterior chamber.[203,204]

What Are the Ocular Complications of Leishmaniasis?

Most commonly the ocular adnexae are involved,[200] but anterior uveitis with elevated IOP and glaucoma have been reported.[201–204]

How Is Malaria Diagnosed?

The diagnosis is made by demonstrating plasmodia in thick blood smears of suspected individuals.[229]

What Are the Ocular Complications of Malaria?

The *Plasmodium* causes hemolysis with anemia, which can lead to blotchy retinal hemorrhages,[216] disc swelling, and vitreous hemorrhage.[205] Bilateral iridocyclitis with elevated IOP[217] and bilateral panuveitis with uveitic glaucoma[216] have been reported.

How Is Trypanosomiasis Diagnosed?

Patients with African trypanosomiasis present with irregular fevers, enlarged lymph nodes, delayed sensation to pain, and skin rash. Definitive diagnosis depends on the demonstration of the parasite in blood, lymph node aspirates, bone marrow, and cerebrospinal fluid.

Acute Chagas' disease should be suspected in any individual from endemic areas with acute febrile illness with lymphadenopathy and myocarditis. Definitive diagnosis is made through documentation of the parasite in the blood.

What Are the Ocular Complications of Trypanosomiasis?

If in Chagas' disease the route of inoculation is through the conjunctiva, Romaña's sign (periorbital edema, conjunctivitis, and dacryocystitis) may be present.[230] A marked postural drop of the IOP has been noted, possibly secondary to changes in the autonomic innervation secondary to the parasitic infection.[220]

Treatment and Management

The treatment of ocular complications of protozoan diseases has to be directed against the underlying parasitic infection. Topical symptomatic therapy (i.e., corticosteroids, cycloplegics, and aqueous suppressants) can be initiated as indicated.

How Is Glaucoma Associated with Toxoplasmosis Treated?

The treatment of ocular toxoplasmosis remains controversial, in particular due to side effects. Some lesions, if far enough in the ocular periphery of an immunocompetent host, can simply be followed up. The most commonly used treatment regimens consist of pyrimethamine, sulfadiazine, and corticosteroids, or pyrimethamine, clindamycin, and corticosteroids. Treatment usually lasts for 3 to 4 weeks, with careful attention to platelet counts if pyrimethamine is used, even though folinic acid is always added to the treatment regimen. Treatment of patients with AIDS cannot be stopped. More recently, atovaquone has been introduced as a therapeutic alternative.[231]

How Is Acanthamoeba Keratitis Treated?

A variety of topically applied therapeutic agents are thought to be effective, including propamidine isethionate, clotrimazole, polyhexamethylen biguanide, and chlorhexidine. Penetrating keratoplasty is preferably avoided in inflamed eyes, but may be necessary in severe cases to preserve the globe or, when the infection has resolved, to restore corneal clarity for optical reasons.[226]

How Is Glaucoma Associated with Leishmaniasis Treated?

The standard therapy for the underlying systemic infection consists of pentavalent antimonials (e.g., sodium stibogluconate or meglumine antimoniate).[232] In addition, liposomal amphotericin B has recently been approved by the United States Food and Drug Administration for treatment as well.[233] The associated uveitic glaucoma can be treated with topical corticosteroids, cycloplegics, and aqueous suppressants as indicated.[201,202]

How Is Glaucoma Associated with Malaria Treated?

Concomitant to systemic antimalarial therapy,[215,229] topical corticosteroids, cycloplegics, and aqueous suppressants can be given as indicated.[216,217]

How Is Trypanosomiasis Treated?

All drugs currently used to treat African trypanosomiasis are very toxic and require prolonged administration. They include eflornithine, suramin, pentamidine isethionate, melarsoprol, and nifurtimox. Two percent of patients treated for central nervous system (CNS) disease experience relapse.

Although numerous drugs have been tried, including those used to treat African trypanosomiasis and leishmaniasis, few have proven to be effective for therapy of Chagas' disease. Nifurtimox and benznidazole have both been tried in conjunction with allopurinol.[234]

Future Considerations

Treatment of uveitic glaucoma secondary to infectious diseases ultimately has to be directed against treatment and prevention of the underlying infection. Vector control,[159] prevention of infection,[215] development of vaccines,[214,235] and development of new chemotherapeutic agents[236,237] are all important in achieving this goal.

Glaucoma Caused by Helminthic Diseases

Definition

What Is Onchocerciasis (River Blindness)?

Onchocerciasis is caused by the parasite *Onchocerca volvulus*. The parasite is spread through bites of the black fly genus *Simulium*. After infection with the larva into connective tissue, it matures to filiform adults and may remain in tissues for years. Clinical manifestations vary according to the parasitic load, previous immunity, and duration of infection. A distressing, pruriginous dermatitis and subcutaneous nodules, which are produced by the inflammatory reaction to dying parasites, are very typical. Female adults produce large amounts of microfilaria that migrate through skin and connective tissue. Once an infected host is bitten, the infectious larvae develop again in the female *Simulium* black fly and the life cycle is completed.[238]

How Does Onchocerciasis Affect the Eye?

Infection with this tissue nematode may cause keratitis with corneal scarring chorioretinitis, optic neuritis, and uveitis with and without glaucoma.

What Is Toxocariasis?

Toxocara canis and *cati* are common intestinal parasites of dogs and cats with humans as natural hosts. Toddlers are usually affected by contact with puppies or eating dirt soiled by infected animals. In infected humans, the larvae spread hematologically and are found in multiple organs. The larvae migrate throughout the body for months or years before they complete their full life cycle, therefore the name *visceral larva migrans* for the disorder.

How Does Toxocariasis Affect the Eye?

Granuloma formation in the posterior segment and diffuse endophthalmitis represent the ocular manifestations. Rare larval migration within the anterior segment can lead to granulomatous uveitis and glaucoma.[239–244]

What Is Cysticercosis and How Does It Affect the Eye?

Cysticercosis results from infection with ingested eggs of the tapeworm *Taenia solium*. Oncospheres are released from the hatching eggs and migrate into the intestinal wall and disseminate via blood and lymph vessels and form

fluid-filled bladder worms (cysticerci) throughout the body.[245,246] Intraocular involvement can cause uveitis and secondary IOP elevation.

Epidemiology and Importance

How Common Is Onchocerciasis?

The habitat of the *Simulium* black fly is around rivers and streams in western and central Africa, central and northern South America, and the Arabian Peninsula. Onchocerciasis is the fourth leading cause of worldwide blindness and is responsible in endemic areas for blindness in millions.[247] Infection in travelers is rare but is being recorded on a regular basis.[238]

How Often Is Onchocerciasis Associated with an Increased IOP and/or Glaucoma?

In Sierra Leone, uveitic glaucoma was reported in 11 of 1,625 individuals with onchocerciasis.[248] In an endemic area for onchocerciasis in Nigeria, optic nerve disease was found in 9% of the population. In 50% of these cases onchocerciasis was thought to be the etiology either through direct involvement of the optic nerve or less likely secondary to uveitic glaucoma.

How Common Is Toxocariasis?

In puppies 2 to 6 months of age, the prevalence of *T. canis* is reported to be 80%. In the U.S. the disease is more prevalent in the south central and southeastern regions. From 10 to 30% of soil samples from public playgrounds and parks are contaminated with *T. canis* eggs.[241]

How Common Is Cysticercosis?

Infection most commonly occurs in areas where pigs and people are in close contact, hygienic standards are low, and undercooked pork is eaten. In some rural areas of Central America, the prevalence of Taeniasis is up to 9.8% of the total population, and autopsy data suggest that up to 3.6% of the population of Mexico have neurocysticercosis.[245,246] Two to seven percent of individuals with cysticercosis have ocular involvement.[249]

Diagnosis and Differential Diagnosis

How Is Onchocerciasis Diagnosed?

Onchocerciasis has traditionally been diagnosed by skin snipping and parasitologic examination; however, screening for palpable skin nodules has been found to be a reliable method to identify communities at serious risk for the disease.[250]

How Is Toxocariasis Diagnosed?

Diagnosis is made clinically with the help of enzyme-linked immunosorbent assays and cytologic diagnosis of intraocular aspirates.[241–243]

How Is Cysticercosis Diagnosed?

Cysticercosis can be diagnosed by documenting parasites in biopsy specimen or fine needle aspirates of palpable subcutaneous nodules. Stool examinations positive for adult *T. solium* constitute supporting evidence. In addition, the diffuse "millet seed" appearance of soft tissue calcifications are also pathognomonic for cysticercosis.[245,246,251]

Treatment and Management

How Is Onchocerciasis Treated?

Until 1987, suramin and diethylcarbamazine were the only drugs available for the treatment of onchocerciasis, and they could not be used for community therapy because of their toxicity and the dosage schedules required. The introduction of annual oral treatment with ivermectin and the donation of this drug by Merck & Co. provided a new opportunity for the safe treatment and control of the disease. Data indicate a significant reduction of microfilarial loads and regression of early lesions of the anterior segment, including iridocyclitis and sclerosing keratitis. Ivermectin was also found to have a beneficial effect on optic-nerve disease and visual field loss.[252]

Concurrent uveitis and elevated IOP is treated with topical antiinflammatory agents and aqueous suppressants as indicated.

How Is Ocular Toxocariasis Treated?

Treatment of ocular toxocariasis can be very difficult. Eradication of the parasite without damage to the ocular tissue due to the dying parasite is the goal. This can be achieved by combining medical therapy (i.e., oral thiabendazole or albendazole) with surgical removal of the parasite. Topical corticosteroids, cycloplegics, and aqueous suppressants are given as indicated to control inflammation and IOP.[241–243]

How Is Cysticercosis Treated?

Treatment consists of medical therapy with praziquantel or albendazole. However, in cases of neurocysticercosis and intraocular involvement, surgical removal of the parasite should be attempted before initiating medical therapy because a severe inflammatory reaction can occur due to the dying parasite. Resulting uveitic glaucoma can be treated with topical steroids, cycloplegics, and aqueous suppressants as indicated.[245,246,253–255]

Additional Helminthic Infections

Many other parasites can infest ocular and intraocular tissues and thus can cause inflammation and secondary IOP elevation with glaucoma. The following parasites have been isolated from intraocular tissues: *Echinococcus multiloc-*

ularis,[256–258] *Loa loa*,[259,260] *Schistosoma*,[261] *Gnathostoma*,[262,263] *Dracunculus*,[264] *Wucheria*,[265,266] and *Paragonimus*.[267,268] Several nematodes, including *Baylisascaris* and *Toxocara*, have been found as a causative agent in diffuse unilateral subacute neuroretinitis.[269–272]

Future Considerations

Screening of communities at risk for parasitic disease, vector and parasite control,[159,244] and education,[273] along with development and supply of new medications to endemic regions worldwide, will be needed to significantly decrease these diseases' incidence and morbidity.[274–279]

GLAUCOMA ASSOCIATED WITH DERMATOLOGIC DISORDERS

Definition

How Can Dermatologic Disorders Cause Glaucoma?

Several dermatologic conditions also affect the ocular structures involved in aqueous outflow, which can cause elevation of the IOP and thus glaucoma if optic neuropathy occurs. Some conditions can cause uveitis and associated elevated IOP with possible resulting uveitic glaucoma. For management, see Figure 16–11.

Which Dermatologic Disorders Can Cause Glaucoma?

Rosacea

Rosacea is a dermatologic condition that frequently affects the eyes. It is characterized by meibomian gland dysfunction and recalcitrant chronic blepharitis. Rosacea can cause keratitis, episcleritis, and iridocyclitis, which in return can cause secondary obstruction of the outflow pathways with resulting elevated IOP.[280]

Vogt-Koyanagi-Harada Syndrome

Vogt-Koyanagi-Harada (VKH) syndrome is associated with bilateral panuveitis and neurologic and dermatologic manifestations. Uveitic glaucoma occurs in every third patient with VKH syndrome[281] (see Chapter 8).

Behçet's Disease

Behçet's disease, which presents with acute hypopyon, iritis, aphthous and genital ulcers, and erythema nodosum in young adults, can also cause uveitic glaucoma in a significant number of adults.

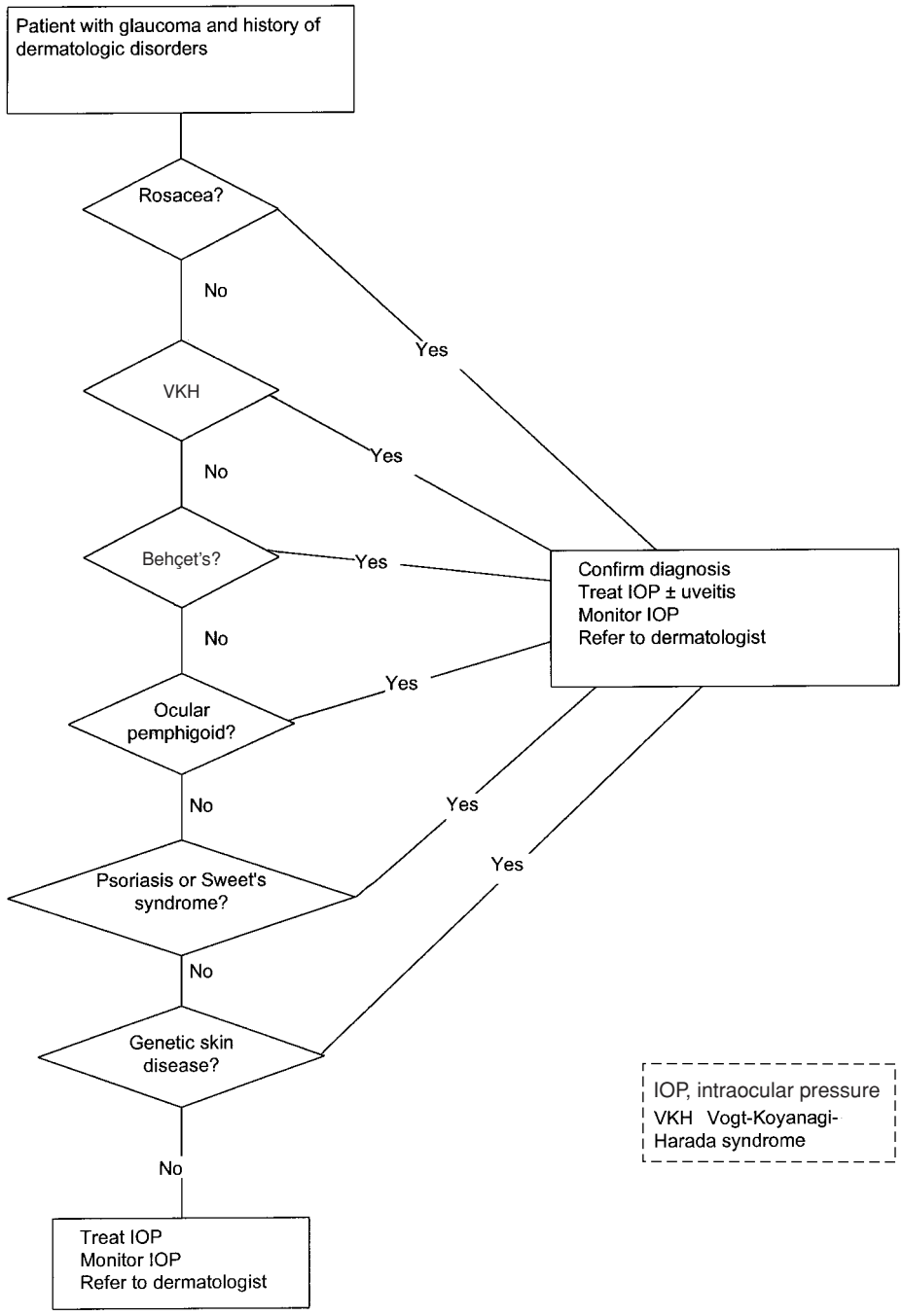

Figure 16-11. Management of a patient with glaucoma and dermatologic disorder.

Ocular Cicatricial Pemphigoid

Ocular cicatricial pemphigoid has also been associated with glaucoma[282]; however, in many cases the disease is probably secondary to the topical antiglau-

Ocular Cicatricial Pemphigoid

Ocular cicatricial pemphigoid has also been associated with glaucoma[282]; however, in many cases the disease is probably secondary to the topical antiglaucoma medications used.[283]

Psoriasis and Sweet's Syndrome

Psoriasis[284] and Sweet's syndrome[285] have been found to cause intraocular inflammation and uveitic glaucoma.

Are There Any Genetic Skin Disorders that Cause Glaucoma?

Rothmund-Thomson syndrome is a rare autosomal recessive disorder with the characteristic skin changes of poikiloderma congenitale, small stature, mental deficiency, and a higher than expected incidence of malignancy. Ocular findings include juvenile cataracts and glaucoma.[286–288] In a series of 22 cases with cutis marmorata, two infants were reported to have glaucoma.[289]

In several phacomatoses, especially Sturge-Weber syndrome, glaucoma can be seen (see Chapter 1).

Are There Other Dermatologic Conditions Known to Cause Glaucoma?

Local and systemic scleroderma,[290–292] oculodermal melanocytosis (nevus of Ota),[293] and juvenile xanthogranuloma (see Chapter 17) are known to cause glaucoma.

Treatment and Management

How Is Glaucoma Associated with Dermatologic Disorders Treated?

Therapy is primarily aimed at the underlying dermatologic condition, if possible. Uveitic glaucoma is treated with antiinflammatory agents and aqueous suppressants as indicated. Infantile glaucoma is generally treated surgically; however, aqueous suppressants may play a role as well.

GLAUCOMA ASSOCIATED WITH NEUROLOGIC DISORDERS

Definition

Certain neurologic disorders may be associated with glaucoma. For management, see Figure 16–12.

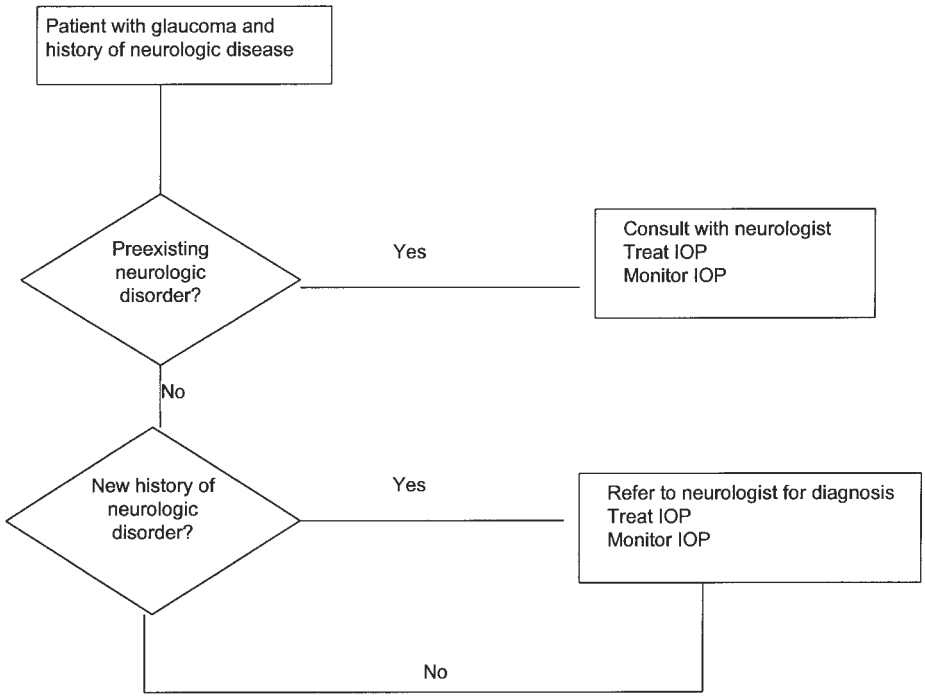

Figure 16-12. Management of a patient with glaucoma and neurologic disorders.

Does the Central Nervous System Regulate the IOP?

A central nervous system influence on the regulation of the IOP has been studied extensively. However, the full extent of its regulatory role has not been established. The IOP can be regulated by neural and/or humoral influences on the rate of aqueous humor formation.[294,295] The role of the hypothalamus in this regulatory process has been studied extensively.[296] A hypothalamic center sensitive to osmotic pressure has been thought to regulate the IOP by efferent optic nerve fibers.[297] Their full role still remains unclear.[298] In addition to that, injection of oxytocin into the cat hypothalamus raises the IOP.[299]

The sympathetic nervous system clearly influences aqueous humor dynamics by influencing the diurnal rhythm of aqueous flow.[300] Autonomic dysfunction in glaucoma has been postulated.[301,302] Centrally acting I1-imidazoline receptor agonists have been shown to lower the IOP.[303] In rabbits, the suprachiasmatic nucleus seems to be involved in the diurnal regulation of the IOP.[304]

In myotonic dystrophy ocular hypotony is quite common.[305] It is controversial whether this is due to a central effect through elevated endogenous circulating gonadotropins resulting in elevated cyclic adenosine monophosphate (AMP) and decreased aqueous humor production[306] or to locally increased uveoscleral outflow.[307]

Epidemiology and Importance

Is Glaucoma Associated with Any Neurologic Disorders?

Although it seems clear that the central nervous system exerts some influence on the regulation of the IOP, no neurologic disorder per se is known to cause glaucoma by the mechanism of IOP elevation. A significant number of patients with Alzheimer's disease also have glaucoma. Again, a causal relationship has not been established.[308] Diurnal IOP variations seem to be higher in patients with open-angle glaucoma.[309]

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Glaucoma Associated with Intraocular Tumors

David J. Bene

Definition

What Is Glaucoma Associated with Intraocular Tumors?

Elevated intraocular pressure (IOP) may be the presenting sign of an intraocular tumor. Typically, this secondary and unilateral glaucoma is dependent on the type, location, and stage of the tumor. The trabecular meshwork can be compromised by several mechanisms resulting in open- or closed-angle glaucoma.

What Types of Intraocular Tumors May Be Associated with Glaucoma?

The most common tumors to be associated with glaucoma are uveal melanoma, retinoblastoma, and metastases to the iris, ciliary body, and choroid. Occasional reports of medulloepithelioma, lymphoma, leukemia, systemic hamartosis (neurofibromatosis, oculodermal melanocytosis, and encephalotrigeminal hemangiomatosis), juvenile xanthogranuloma, and nevus of Ota are found in the literature.[1–10]

When Does One Suspect that Glaucoma Is Secondary to an Underlying Intraocular Tumor?

Intraocular tumor is suspected if there is elevated IOP and asymmetry of the optic nerves. Shields et al[2] established 23 mm Hg as the arbitrary lower limit for elevated IOP. A detailed history to elicit the presence of systemic cancer (especially breast, lung, or leukemia), skin lesions (neurofibromas, café-au-lait spots, or nevus of Ota), or buphthalmos may lead to the suspicion of ocular

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involvement. A clinical examination including slit-lamp biomicroscopy, gonioscopy, and indirect ophthalmoscopy may reveal the presence of an atypical mass.

Epidemiology and Importance

What Age Groups Develop Glaucoma Associated with Intraocular Tumors?

There are many intraocular tumors that develop during infancy and childhood that may be associated with glaucoma. Juvenile xanthogranuloma[10] is usually apparent in infants and young children. It is rarely seen in adults. It is a benign histiocytic proliferation commonly of the skin with formation of Touton giant cells. However, the iris is the most common extracutaneous site and is frequently associated with hyphema. This tumor is a highly vascularized tan-yellow-to-brown lesion within the iris. Frequently, this is a self-limited tumor that may regress with time.

Retinoblastoma, the most common childhood intraocular malignancy, is associated with inactivation of both alleles of the retinoblastoma gene on the long arm of chromosome 13. Undetected at birth or in adults, retinoblastoma usually presents in unilateral cases at age 23 months and bilaterally at age 1 year.[11] The cumulative lifetime incidence of retinoblastoma is approximately 1/15,000 individuals. Inheritance of retinoblastoma can be a result of somatic or germinal factors. However, the majority of retinoblastoma cases are sporadic in nature.[12] Histologically, retinoblastomas are recognized by the presence of Flexner-Wintersteiner rosettes. Retinoblastoma has a strong propensity to invade optic nerve, choroid, and scleral emissary canals. Clinically, Ellsworth[13] described leukocoria and strabismus as the most frequent initial presentations of retinoblastoma; glaucoma occurred initially in 7% of eyes.

Neurofibromatosis is the most common phakomatosis. This neuroectodemal tumor with autosomal dominant inheritance may involve multiple organs. Neurofibromatosis is classified as type I or type II. Neurofibromatosis type I is peripheral, mapped to chromosome17q11, and is associated with multiple cutaneous café-au-lait spots, presence of optic nerve glioma, multiple Lisch nodules, and inguinal and axiliary freckling.[14] Neurofibromatosis type II is central, mapped to chromosome 22q22, and is associated with acoustic neuromas, peripheral nerve sheath tumors, and posterior subcapsular cataracts.[15] Neurofibromatosis may present in the first year of life as a congenital glaucoma especially when associated with eyelid involvement or ipsilateral facial hemihypertrophy. François syndrome[14] is a type of peripheral neurofibromatosis consisting of unilateral buphthalmos, homolateral facial hemihypertrophy, and homolateral plexiform neuroma of the eyelid.[16,17]

Medulloepithelioma is a rare congenital tumor typically diagnosed at 2 to 4 years of age, but it may appear in adults as well.[18] Clinically, when medulloepithelioma involves the iris, a tan-to-pink mass replaces the normal peripheral iris and invades the angle. In contrast, when medulloepithelioma arises from the ciliary body, a tan-to-white lesion may be observed within the pupil by indirect ophthalmoscopy or slit-lamp examination. Absences of zonules, lens coloboma, and cataract have been associated findings.[19] Histologically, this lesion is composed of primitive neuroectodermal cells arising from the non-

pigmented epithelium of the ciliary body. A variety of atypical histologic findings may be present including cartilage and striated muscle.

Nevus of Ota is a unilateral accumulation of melanocytes within the dermis and is associated with ipsilateral pigmentation of the lids and periorbita. This hamartoma is distributed in the ophthalmic and maxillary divisions of the fifth cranial nerve. Pigmentation may be present in the iris, cornea, fundus, optic disc, sclera, and conjunctiva. Most cases are sporadic; however, in some familial cases an autosomal recessive inheritance is present. There is a 4:1 female to male predilection for the occurrence of nevus of Ota.[20] The associated glaucoma, more frequent in blacks and Orientals, usually develops in the age group of 20 to 40 years. As shown by Gonder et al,[21] whites with nevus of Ota rarely develop glaucoma.

Iris melanocytoma is rare with only incidental case reports in the literature.[7,8,21] This benign tumor tends to occur on the inferior iris typically in the fourth decade of life. However, this tumor may undergo malignant transformation. Melanocytomas are frequently present in black or dark-complexioned individuals. Ocular pain, injection, and keratitic precipitates may be the initial presenting signs. Histologically, this tumor is composed of large uniform polygonal cells with small, bland nuclei with intensely pigmented cytoplasm.[8] Association with glaucoma has been reported by Shields et al[19] in a 23-year-old and by Gonder et al[21] in a 7-year-old white girl and in similar patients in their second and third decade of life.[21] Croxatto et al[22] reported a case of optic disc melanocytoma associated with angle-closure glaucoma in a 44 year old, and there are other reports in the literature.[23–25] Iris melanomas usually develop in the fourth decade, whereas most posterior uveal melanomas are diagnosed in patients after the fifth decade.[26]

Systemic large-cell lymphoma occurs in middle-aged or older patients; it is a form of non-Hodgkin's lymphoma and is a systemic malignancy. The eye is infrequently involved but can be associated with glaucoma.[27] Clinically, large cell lymphoma presents as a bilateral nongranulomatous uveitis that is eventually recalcitrant to topical steroids. Lymphoma cells massively infiltrate the uveal tract and vitreous cavity.

Metastatic tumors are the most common intraocular malignancies. Approximately 10% of patients who die of cancer have evidence of ocular or orbital metastasis, with the choroid being the most common metastatic site.[28,29] Metastasis occurs most frequently at ages 40 to 70 from primary cancer of the breast, lung, or gastrointestinal or genitourethral systems.[30] However, metastatic cancer may present in children and adults from leukemia. Leonardy et al[4] histologically examined the eyes from 135 patients who died of leukemia. Leukemic ocular infiltrates were found in 31.1% of the patients with the choroid as the most frequently involved site. Metastatic tumors may present to the iris but it is rare. Shields et al[31] found that of 512 patients with uveal metastasis only 7.8% had iris involvement. Bronchial carcinoid, breast, and lung carcinomas were the most common primary malignancy. These patients complained of blurred vision, redness, and ocular pain. Clinically, iris metastases are fleshy, yellow-white friable masses that release tumor cells into the anterior chamber. It has been reported that the incidence of a secondary glaucoma is 38% with patients in iris metastasis. Iris metastasis is usually seen in adults, but metastatic neuroblastoma is seen in children.[31]

What Is the Incidence of Glaucoma Associated with Various Intraocular Tumors?

The association of glaucoma with intraocular tumors was reported as early as 1896 by Marshall.[32] The prevalence of tumor-associated glaucoma is largely dependent on tumor type, location, and stage,[7,33] as well as on the investigator's study design. Comparison of various studies produces varied results often dependent on analysis of histologic specimens versus clinical data. Yanoff[34] studied the histologic sections of 96 eyes enucleated for melanoma, comparing the 19 eyes with glaucoma (both open- and closed-angle forms) to the 77 without glaucoma. His data confirmed the increased risk of glaucoma in large posterior tumors with total retinal detachment, as well as the increased incidence of glaucoma with anterior (iris and ciliary body) melanomas. Ciliary body melanoma alone was not an increased risk factor for glaucoma.

Shields et al[2] retrospectively evaluated the intraocular pressure of 2,704 eyes with intraocular tumors that were referred to Wills Eye Hospital from 1974 to 1986. Only those eyes with IOP elevation due to tumor and with pressures greater than 23 mm Hg were included in the study. Only 5% of the eyes with tumors presented with glaucoma (Table 17–1).

Uveal Melanoma

Of the 2,111 eyes with uveal melanoma in the series from Shields et al,[2] 3% had secondary glaucoma: 7% of iris melanomas, 17% of ciliary body melanomas, and 2% of choroidal melanomas. Allaire et al[35] and others have described ring melanomas, a rare variant of melanoma involving diffuse, circumferential neoplastic invasion of the iris, ciliary body, and angle. Glaucoma is most often associated with ring melanoma and this secondary glaucoma is a result of direct neoplastic invasion of the chamber angle or neovascularization. Diagnosis of a ring melanoma might be delayed because there is no visible mass on slit-lamp examination, and an intraocular mass may not be detected with B-scan ultrasonography. Heterochromia iridis, increased pigmentation of the trabecular meshwork, and glaucoma are the most frequently reported clinical findings associated with ring melanoma. Although pigmentary dispersion glaucoma and ring melanoma both exhibit increased pigmentation of the trabecular meshwork, pigmentary glaucoma is usually a bilateral process. Krukenberg spindles (pigment on the endothelium) and iris transillumination defects are not clinical signs in ring melanoma.[36] Limbal extrascleral nodules may be the first presenting signs of ring melanoma. Ultrasound biomicroscopy may be an important ancillary tool to define this anterior segment tumor. The incidence of ring melanoma is unknown, and therefore the incidence of glaucoma is difficult to determine.[35] Studies on the prevalence of glaucoma in uveal melanoma report variable statistics. Some reports are reviews of histologic enucleated specimens versus the incidence of intraocular tumors presenting to a glaucoma or oncology clinic. As Shields et al[2] indicate, large melanomas with glaucoma are most likely enucleated by the primary ophthalmologist, and only tumors amenable to irradiation are referred to their institution for further treatment. Recent statistics may also be altered by the widespread use of indirect ophthalmoscopy leading to earlier diagnosis of smaller tumors.

Table 17–1. Eyes with Intraocular Tumors and Secondary Intraocular Pressure (IOP) Elevation

Tumor	Total No. of Eyes	No. of Eyes with IOP Elevation (%)	
Uveal Melanoma			
Iris melanoma	102	7	(7)
Ciliary body melanoma	96	16	(17)
Choroidal melanoma	1,913	32	(2)
Total	2,111	55	(3)
Uveal Metastasis			
Iris metastases	11	7	(64)
Ciliary body metastases	3	2	(67)
Choroidal metastases	242	3	(1)
Total	256	12	(5)
Retinoblastoma	303	51	(17)
Miscellaneous Intraocular Tumors			
Lymphoma	11	3	(27)
Leukemia	11	1	(9)
Benign reactive lymphoid hyperplasia choroid	2	0	(0)
Medulloepithelioma (ciliary body)	2	2	(100)
Adenoma, pigment epithelium (iris)	2	1	(50)
Adenoma, pigment epithelium (ciliary body)	1	0	(0)
Adenoma, nonpigment epithelium (ciliary body)	4	0	(0)
Melanocytoma (iris)	1	1	(100)
Total	34	8	(24)
Overall Total	**2,704**	**126**	**(5)**

With permission from Shields CL, Shields JA, Shields MB, et al: Prevalence and mechanisms of secondary intraocular pressure elevation in eyes with intraocular tumors. Ophthalmology 1987;94(7): 839–846.

Metastases

Metastases to the eye most commonly occur to the choroid centrally. In Shields et al's[2] series of 256 eyes manifesting uveal metastases, only 5% developed glaucoma. The majority of these uveal metastases associated with glaucoma involved the iris and ciliary body. Metastases to the iris and ciliary body were less frequent in occurrence but were increasingly associated with glaucoma in 64% and 67% of cases, respectively. In 242 cases of choroidal metastases, only 1% had elevated IOP greater than 23 mm Hg. Iris and ciliary body melanoma have elevated IOP secondary to direct tumor invasion of the angle; choroidal melanoma has elevated IOP resulting in angle closure from choroidal or retinal detachment.[2]

Lymphoma/Leukemia

Sporadic case reports associate glaucoma with intraocular lymphoma, leukemia, metastatic melanoma, multiple myeloma, histiocytosis X, and myelodysplastic syndrome. In Shields et al's[2] survey, which consisted of 2,704 eyes with intraocular tumors, there were 11 eyes with lymphoma and leukemia each. Glaucoma was associated in 27% and 9% of the eyes with lymphoma and leukemia, respectively.

Retinoblastoma

Reports of glaucoma associated with retinoblastoma vary from 2 to 23%.[37,38] In Shields et al's[2] 12-year study including 303 eyes with retinoblastoma, 17% developed glaucoma. Elevated IOP usually developed in advanced tumors occupying most of the vitreous cavity.

Medulloepithelioma

Broughton and Zimmerman[18] described 56 cases of medulloepithelioma of which 46% were associated with glaucoma. Shields et al's[2] included two medulloepitheliomas among 2,704 intraocular tumors; both cases had elevated IOP.

Melanocytoma

The incidence of melanocytoma complicated by glaucoma is unknown; there are case reports of iris melanocytoma and an even rarer association of optic nerve melanocytoma and glaucoma.[8,22]

Neurofibromatosis

Neurofibromatosis is the most common phakomatosis and its frequency in the general population is approximately one in 3,500.[39] Neurofibromatosis type I is more common, and its ophthalmic findings include Lisch nodules, plexiform neurofibromas of the eyelids, diffuse choroidal thickening, prominent corneal nerves, multifocal choroidal nevi, optic nerve gliomas, meningioma, and retinal astrocytic hamartoma. Sachsalber[40] described the association of neurofibromatosis and glaucoma as early as 1897.

Congenital glaucoma may be present in patients with neurofibromatosis particularly with plexiform involvement of the eyelid.[16] Neurofibromatosis may be associated with partial gigantism or segmentary hypertrophy, especially facial hemihypertrophy. The triad of unilateral buphthalmos, homolateral facial hemihypertrophy, and homolateral plexiform neuroma of the eyelid is known as François syndrome.[17] This is the most common presentation of buphthalmos in neurofibromatosis.

Nevus of Ota

Case reports of glaucoma associated with nevus of Ota are found in the literature.[20] The incidence may be as high as 10% of involved eyes.[41]

Juvenile Xanthogranuloma

Sporadic cases of juvenile xanthogranuloma of the iris, associated with glaucoma, are found in the literature.[10] Diagnosis of juvenile xanthogranuloma is bimodal in nature: peak incidence occurs before 1 year of age and between 20 and 30 years. There is a male/female ratio of 4:1.[42]

Diagnosis and Differential Diagnosis

What Is the Differential Diagnosis and Distinguishing Features of Unilateral Glaucoma Not Associated with Intraocular Tumors?

Friedman[1] characterized unilateral glaucoma by mechanism as open- and closed-angle forms. In the open-angle type, outflow was impaired either by accumulated material in the angle or from compromised angle structures. With hyphema, obstruction of the angle occurs by macrophages that have engulfed hemosiderin. Similarly, in uveitis inflammatory cells block the angle. Fuchs' heterochromic iridocyclitis is typified by cataract, low-grade iridocyclitis, heterochromia, fine neovascularization of the angle, and glaucoma in a white, quiet-appearing eye. Phacolytic glaucoma characteristically occurs with a hypermature lens and is possibly associated with trauma; macrophages laden with lens material are seen as iritis or hypopyon. Pseudoexfoliation is an autosomal dominant disorder with incomplete penetrance and variable expressivity affecting patients 60 to 80 years of age. With gonioscopy, exfoliated debris can be seen on the iris surface and in the angle; iris transillumination defects and "hoarfrost" on the lens can be visualized. Pseudoexfoliation is unilateral 50% of the time and is associated with glaucoma in 70% of patients (Table 17–2).

Friedman[1] further subdivided unilateral open-angle glaucoma into a subgroup with defective outflow channels. Hemosiderosis bulbi resulting from intraocular hemorrhage or siderosis bulbi resulting from retained iron containing

Table 17–2. Unilateral Nonintraocular Tumor Glaucomas (Secondary) Open-Angle Type: Cells or Debris in the Angle

Hyphema
Uveitis
Iridocyclitis (e.g., Fuchs' heterochromic)
Glaucomatocyclitic crisis
Phacolytic glaucoma
Following lens rupture
Hemolytic glaucoma
Pigmentary glaucoma
Malignant glaucoma
Pseudoexfoliation

With permission from Friedman AH: Clinicopathological correlations in unilateral glaucoma. Bull NY Acad Med 1979;55(3): 338–345.

Table 17–3. Unilateral Nonintraocular Tumor Glaucomas (Secondary) Open-Angle Type: Damaged Outflow Channels

Hemosiderosis (or siderosis) bulbi
Trauma
Direct effect
Postcontusion angle deformity
With endothelialization
Chymotrypsin induced
Steroid induced
Postinflammatory
Associated with extraocular disease (e.g., cavernous sinus thrombosis)

With permission from Friedman AH: Clinicopathological correlations in unilateral glaucoma. Bull NY Acad Med 1979;55(3): 338–345.

intraocular foreign body may lead to heterochromia, glaucoma, and visual loss from retinal toxicity. Trauma may produce unilateral glaucoma by direct injury to the angle or angle recession (Table 17–3).

Unilateral angle-closure glaucoma occurs in association with peripheral anterior synechiae (PAS). Rubeosis iridis, causing the formation of fibrous tissue in the angle, can result from underlying nonocular vascular diseases (carotid disease, aortic arch syndrome, giant cell arteritis, or carotid/cavernous fistula), inflammatory diseases (after endophthalmitis, irradiation, or uveitis), or primary retinal diseases (Coats' disease, persistent hyperplastic primary vitreous, Norrie's disease, retinopathy of prematurity, Leber's disease, diabetes mellitus, or retinal detachment). With down-growth syndromes, epithelialization of the anterior chamber occurs following injury or surgery. When epithelial down-growth occurs, a thin, gray membrane may proliferate on the posterior corneal surface, within the anterior chamber angle and on the anterior iris surface. Additional sources of unilateral glaucoma are serous cysts of the iris, pearl growths, and endothelial cell growth (Table 17–4).

Table 17–4. Nonintraocular Tumor Unilateral Glaucomas (Secondary) Angle-Closure Type: Peripheral Anterior Synechiae

With rubeosis iridis
Without rubeosis iridis
Chronic angle-closure glaucoma
Lens induced
Swollen lens
Dislocated lens
Flat chamber
Essential iris atrophy
Chandler's syndrome
Iris nevus syndrome
Epithelial invasion of the anterior chamber
Endothelialization of the anterior chamber

With permission from Friedman AH: Clinicopathological correlations in unilateral glaucoma. Bull NY Acad Med 1979;55(3): 338–345.

What Are the Presenting Signs and Symptoms?

Iris melanomas are usually slow-growing, well-defined lesions that may be pigmented or amelanotic. The diffuse type of iris melanoma is associated with unilateral acquired heterochromia and ipsilateral glaucoma. Thickening of the iris stroma with angle invasion may be seen gonioscopically. Spontaneous hyphema may also occur.[3]

Necrotic iris melanocytoma also causes secondary glaucoma and heterochromia. Differentiation of iris melanocytoma from iris melanoma may be difficult clinically and require histologic confirmation.[7]

Ciliary body melanomas appear as brown masses in the ciliary body. These tumors may grow circumferentially extending around the ciliary body (ring melanoma). Ciliary body melanomas may present with either angle-closure, open-angle, or neovascular glaucoma.

Choroidal melanoma is a variably pigmented mass that may be mushroom-shaped and associated with retinal detachment. Angle closure may develop as the tumor enlarges; alternatively, rubeosis iridis and neovascular glaucoma may ensue.

Most commonly ocular metastases occur to the posterior pole as creamy-colored lesions with an overlying (nonrhegmatogenous) serous retinal detachment. Intractable angle-closure glaucoma can develop with diffuse involvement of the posterior uvea. The anterior uvea is much less frequently involved with metastases, but has greater propensity to develop glaucoma either of the closed- or open-angle forms. These anterior metastatic lesions appear as single or multinodular fleshy masses on the iris. They are friable, frequently seeding tumor cells into the angle, creating inflammation or pseudohypopyon. Rubeosis iridis is often associated. Ocular metastases may be the initial presentation of the malignancy. Shields et al[31] report that 32% of patients have no history of a primary cancer when the diagnosis of iris metastasis was made. Frequent clinical findings in metastatic iris tumors include secondary glaucoma (38%), prominent epibulbar injection (40%), irregular pupil (60%), hyphema (15%), pseudohypopyon (10%), and choroidal metastasis (35%). The size of metastatic iris tumors ranged from $1 \times 1 \times 0.5$ mm to $12 \times 6 \times 3$ mm. The most common primary sites are breast and lung followed by gastrointestinal tract, kidney, thyroid, and skin.[29,31,43,44]

Retinoblastoma may present as leukocoria, strabismus, or glaucoma. The differential diagnosis of retinoblastoma is listed in Table 17–5. Classically, retinoblastoma occurs in infants or very young children. However, it may also occur in older children and adults. In one review of 400 consecutive cases of retinoblastoma, 8.5% of the patients were 5 years or older at the time of diagnosis.[45] Clinically, retinoblastoma may initially present as acute orbital cellulitis. Although the presence of intraocular calcium is suggestive of retinoblastoma, the absence of calcium does not exclude this tumor. Diffuse infiltrating retinoblastomas may not exhibit calcification or distinct mass.[46,47] Both endo- and exophytic growth patterns may be associated with glaucoma that is usually seen only in the advanced stages of the tumor. Both angle-closure and neovascular glaucoma may develop.[48,49]

Medulloepithelioma of the iris or ciliary body appears as a solid or cystic grayish mass that is frequently associated with PAS and a shallow anterior chamber.

Table 17–5. Classification of Conditions That Can Simulate Retinoblastoma

Hereditary conditions
Norrie's disease
Congenital retinoschisis
Incontinentia pigmenti
Dominant exudative vitreoretinopathy
Developmental abnormalities
Persistent hyperplastic primary vitreous (PHPV)
Congenital cataract
Coloboma
Retina dysplasia
Congenital retinal fold
Myelinated nerve fibers
Morning glory syndrome
Congenital corneal opacity
Inflammatory disorders
Ocular toxocariasis
Congenital toxoplasmosis
Congenital cytomegalovirus retinitis
Herpes simplex retinitis
Peripheral uveoretinitis
Metastatic endophthalmitis
Orbital cellulitis
Tumors
Retinal astrocytic hamartoma
Medulloepithelioma
Glioneuroma
Choroidal hemangioma
Combined retinal hamartoma
Leukemia
Miscellaneous
Coats' disease
Retinopathy of prematurity
Rhegmatogenous retinal detachment
Vitreous hemorrhage
Perforating ocular injury

With permission from Shields JA, Shields CL, Parsons HM: Review. Differential diagnosis of retinoblastoma. Retina 1991;11:232–243.

Leukocoria or hyphema may also be observed. Glaucoma occurs from direct infiltration of the angle structures or rubeosis iridis. These tumors are seen at an older age than retinoblastoma and are typically not associated with calcification.[6,18]

What Are the Mechanisms for the Development of Secondary Glaucoma with Intraocular Tumors?

As with all glaucoma, either open- or closed-angle types can develop. Early studies published by Marshall[32] in 1896 described angle closure in large choroidal tumors causing compression of the iris root into the angle and com-

promise of the angle structures by forward displacement of the lens/iris diaphragm. Other authors confirmed this mechanism of angle closure in ciliary body melanoma.[50] Friedman[1] noted PAS most frequently secondary to rubeosis iridis, as an invariable association to angle-closure glaucoma. Neoplastic sources of rubeosis iridis were uveal melanoma, retinoblastoma, and metastatic cancer. Yanoff[34] studied the histopathology of 19 eyes with melanoma and associated glaucoma. In the group with angle closure, PAS was a consistent finding, whereas iris bombé, posterior synchiae, rubeosis iridis, and diffuse iris melanoma were variably present. In the group with open-angle glaucoma, aqueous drainage was obstructed. This occurred from seeding of tumor cells into the anterior chamber, by invasion of angle structures (as in ring melanomas), or by melanin-laden macrophages blocking the angle (melanomalytic glaucoma). Shields and Proia[51] described neovascular glaucoma occurring with isolated rubeosis iridis in iris melanoma without direct tumor involvement of the angle. A secondary glaucoma associated with spontaneous hyphema may also occur (Fig. 17–1).

Iris Melanoma

Iris melanoma most frequently directly invades the trabecular meshwork, but tumor seeding, melanin granules, or macrophage laden with melanin may obstruct the angle; secondary glaucoma from hyphema or rubeosis iridis has also been reported.[33,35] A case report of iris ring melanoma associated with unilateral glaucoma and mistaken for unilateral pigmentary glaucoma cautions one in diagnosing atypical but increased angle pigmentation.[36]

Ciliary Body Melanoma

Ciliary body melanoma may cause angle-closure glaucoma by compressing the iris root into the angle or by forward displacement of the lens-iris diaphragm by the expanding mass creating a pupillary block.[52] Iris bombé subsequently develops followed by formation of PAS and a secondary angle closure. PAS and angle closure may also develop as a result of rubeosis iridis. Alternatively, invasion of the angle by tumor or seeding of neoplastic cells or melanin granules from necrotic tumors may lead to mechanical obstruction of the trabeculum and open-angle glaucoma.[2]

Choroidal Melanoma

Choroidal melanoma is associated with glaucoma by iris and angle neovascularization, tumor necrosis-induced inflammation, pigment dispersion, or anterior displacement of the lens-iris diaphragm. This is a mass effect of the tumors with or without a retinal detachment or swelling of the lens.[2,53]

Iris and Ciliary Body Metastases

Metastatic tumors to the iris and/or ciliary body produce glaucoma by invading the angle structures or by covering them with sheets of tumor cells. Other mechanisms include pigmentary dispersion and hemolytic, uveitic, and neovascular forms of glaucoma.

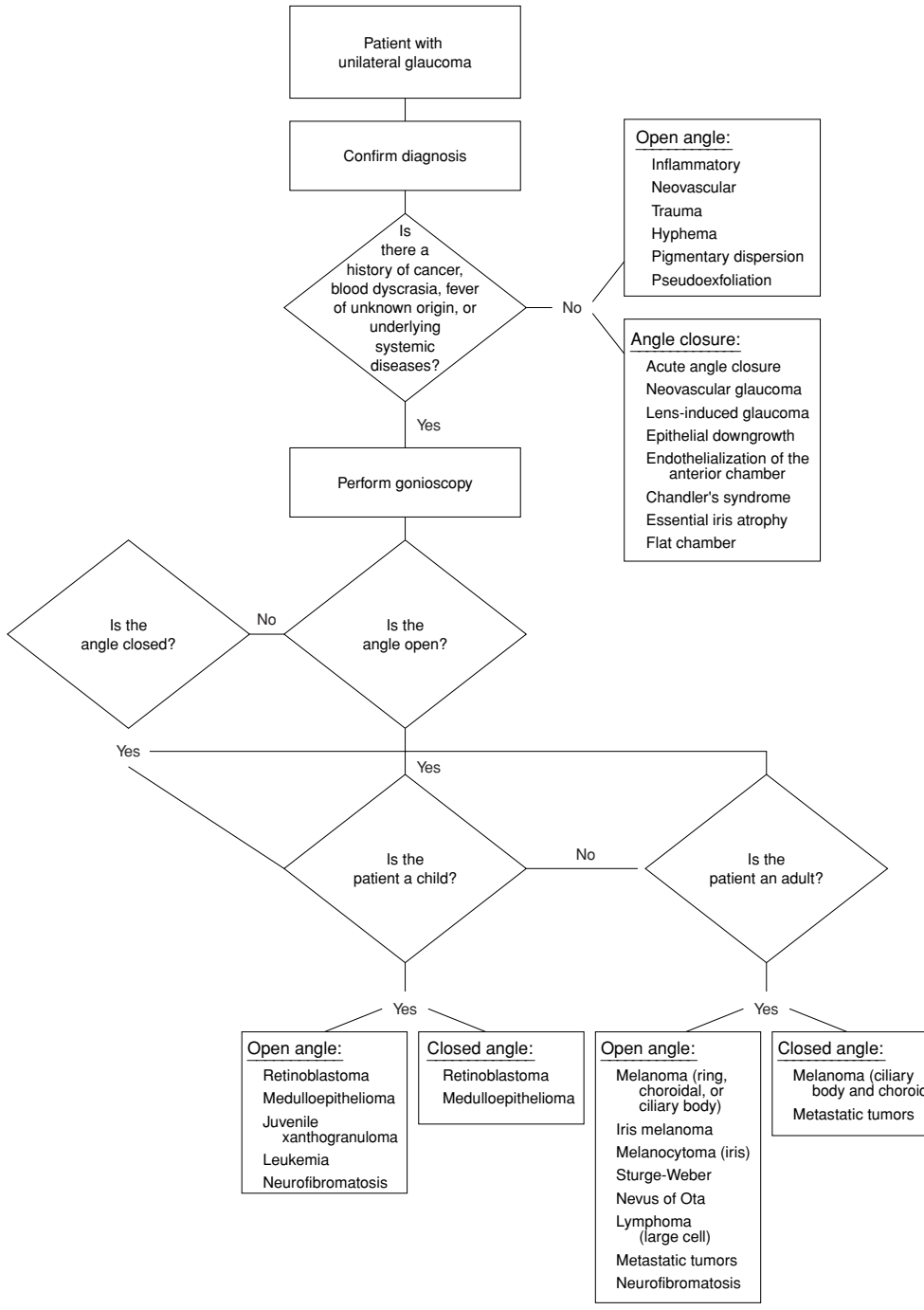

Figure 17–1. Differential diagnosis of a patient with glaucoma associated with intraocular tumors

Choroidal Metastases

In contrast, choroidal metastases affect IOP only with large mass size that is associated with choroidal or total retinal detachment. Subsequently, angle closure develops from displacement of the lens-iris diaphragm.[2,44] The formation of PAS may also lead to angle closure.[54]

Leukemia

Glaucoma may occur in leukemia by direct infiltration of angle structures, or be associated with hypopyon or hyphema.[55] Massive subretinal or choroidal hemorrhage has reportedly been associated with cases of angle closure.[2,4,56–58]

Lymphoma

Intraocular lymphoma may directly infiltrate the uveal tract or be associated with a nongranulomatous uveitis causing a secondary IOP elevation.[59]

Retinoblastoma

Many studies of retinoblastoma confirm that iris neovascularization is the most frequent cause of glaucoma.[2] Angle closure from anterior displacement of the lens-iris diaphragm secondary to massive, exudative retinal detachment may occur. Less frequently, there is tumor seeding or shedding of necrotic tumor cells into the anterior chamber, uveitis, or hyphema.[13,38]

Medulloepithelioma

Histopathologic specimens of medulloepithelioma associated with glaucoma confirm the presence of rubeosis iridis, PAS, and shallow anterior chamber.[18] Narrow-angle glaucoma may also be produced by the large mass effect posteriorly causing forward displacement of the lens-iris diaphragm. Direct infiltration of the angle by tumor cells or hyphema may cause a form of open-angle glaucoma.[6,18]

Iris Melanocytoma

Iris melanocytoma may be associated with glaucoma. Shedding of tumor cells or necrosis of the tumor with pigment dispersion into the anterior chamber compromises the trabecular meshwork.[7,23,60] Rare reports of optic disc melanocytoma describe glaucoma resulting from the massive tumor size causing forward displacement of the lens-iris diaphragm and angle closure.[22]

Juvenile Xanthogranuloma

This tumor may be associated with either a vascular iris or ciliary body mass that produces glaucoma due to its hemorrhagic or inflammatory propensity. Open-angle glaucoma occurs from hyphema, uveitis, or even histiocytic invasion of the angle.[18,61]

Sturge-Weber

This syndrome is characterized by cutaneous facial nevus flammeus in the trigeminal nerve distribution, ipsilateral diffuse cavernous hemangioma of the choroid, and ipsilateral meningeal racemose hemangioma. The choroidal hemangioma associated with Sturge-Weber is not the direct cause of the frequently associated glaucoma. The etiology of the glaucoma is equivocal and may be multifactoral. Possible mechanisms include vascular or mechanical etiologies. It has been possibly attributed to anomalous development of the angle, neovascularization of the trabecular meshwork, or small arteriovenous fistulas in the episcleral vessels causing elevated venous pressure.[62–66] Histologic evidence reveals a poorly developed scleral spur and thickened uveal meshwork; the iris root is anteriorly inserted on the trabecular meshwork base.[62] In addition, incomplete and posterior displacement of the Schlemm's canal has been reported.[63] It is hypothesized that the etiology of elevated IOP in Sturge-Weber is a result of combined developmental angle anomalies and elevated episcleral venous pressure mechanisms; ultimately, these mechanisms yield ultrastructural and functional changes in the trabecular meshwork.[67]

Neurofibromatosis

In neurofibromatosis, glaucoma may occur by a variety of postulated mechanisms: (1) neurofibromas may infiltrate the angle, (2) increased secretion of the ciliary body may occur from paralysis of the ciliary nerves, (3) nodular thickening of the ciliary body and choroid may close the angle, (4) rubeotic-like tissue in the angle may create PAS, and (5) an anomalous angle may develop with aplastic or incompletely formed Schlemm's canal. Buphthalmos may occur with normal IOP as a form of regional gigantism.[17,68,69]

Nevus of Ota

The ipsilateral open-angle glaucoma associated with oculodermal melanocytosis (nevus of Ota) may be secondary to tumor (melanoma of the iris, ciliary body, or choroid), inflammation, or melanocytic infiltration of the aqueous outflow channels.[9,20]

What Is Melanomalytic Glaucoma?

Melanin from a necrotic melanoma is engulfed by macrophages that obstruct the trabecular meshwork. Additionally, melanin may be phagocytosed by trabecular endothelial cells.[34,70,71]

What Is the Differential Diagnosis of Heterochromia Associated with Unilateral Glaucoma and Intraocular Tumor?

Nevus of Ota, retinoblastoma, iris melanoma, iris metastases, ring melanoma, and iris medulloepithelioma present with heterochromia and unilateral glau-

coma. Nevus of Ota is congenital in nature. Retinoblastoma and iris medulloepithelioma are commonly diagnosed in the first decade of life. In contrast, iris melanoma, ring melanoma, and iris metastases occur in adults.

What Factors Influence the Likelihood of Glaucoma Developing in Melanoma?

Yanoff[52] reported on 19 eyes with melanoma and associated glaucoma. He concluded that the size and location of the tumor, the nature of the lesion, and associated retinal detachment were the risk factors for developing glaucoma. Increased prevalence of glaucoma occurred with anterior melanomas involving only the iris, combined iris, and ciliary body, or with large posterior tumors accompanied by total retinal detachment. In Shields and Klintworth's[33] review of 11 consecutive anterior uveal melanomas, there was a correlation between elevated IOP and tumor involvement of the iris and angle. Tumor necrosis with dispersion of melanin and/or melanin-laden macrophages predisposes to melanomalytic glaucoma. Furthermore, the presence of rubeosis iridis or PAS increases the risk of glaucoma. The importance of melanoma type is demonstrated by the consistent association of glaucoma in ring melanoma[35] (Table 17–6).

What Diagnostic Modalities Are Important in the Evaluation and Examination of Glaucoma Secondary to Underlying Intraocular Tumor?

A thorough history, including breast masses, skin lesions, cough, lung tumor, gastrointestinal problems, changes in weight, and fever of unknown origin, is important to elicit. Previous surgeries, underlying systemic diseases or vascular problems, blood dyscrasias, tuberculosis, evidence of malignancy, and previous chemotherapy or other cancer treatment should be noted in the medical record. Previous ocular surgeries or problems must also be recorded.

To perform a full clinical examination in children, anesthesia may be necessary. The importance of the clinical exam is emphasized by Yanoff,[52] who reports that melanoma of the iris associated with glaucoma usually can be

Table 17–6. Malignant Melanoma Glaucoma Mechanism

Open Angle
Seeding of the anterior chamber
Infiltration of the angle
Necrosis of tomor with phagocytosis (melanomalytic)
Angle Closure
Rubeosis iridis
Compression of the anterior segment
Diffuse iris nevus or melanoma

With permission from Friedman AH: Clinicopathological correlations in unilateral glaucoma. Bull NY Acad Med 1979;55(3): 338–345.

diagnosed by clinical exam. Additionally, he cautions that an eye with opaque media and glaucoma not responding to conventional therapy must be suspect for undiagnosed melanoma. The ocular examination should include IOP measurements, biomicroscopy, gonioscopy, and dilated fundus exam. The exclusion of tumor associated with glaucoma or the risk of glaucoma with a known intraocular tumor needs to be assessed. All eyes with rubeosis iridis should undergo gonioscopy to exclude a mass lesion in the angle. The angle should be studied for patterns of pigmentation, configuration, depth, and evidence of previous inflammation such as PAS. The iris surface should be examined for rubeosis iridis, heterochromia, ectropion uveae, and mass lesions. Translucent, gelatinous nodules are typical of metastases; the hallmark of neurofibromatosis is the variably colored dome-shaped stromal iris elevations known as Lisch nodules. Variably pigmented iris lesions are present in melanoma and melanocytoma.

Stereo slit-lamp and fundus photographs are important for documentation and growth observation. B-scan ultrasound may aid in defining the solid or cystic nature of a lesion, the nodularity or dimensions, and the characteristic reflectivity. This technique may be used to exclude possible extension of an anterior chamber mass from the ciliary body. High-resolution (50 MHz) ultrasound biomicroscopy (UBM) has been used in eyes with impaired visualization of the anterior segment. Lanzl et al[72] described the use of this technique in an eye with metastatic cancer, hypopyon, and elevated IOP. Excisional biopsy of an iris mass, by peripheral or sector iridectomy, with frozen sections may assist in the differentiation of iris nevus versus melanoma. Confirmation of melanin granules (from necrotic tumor) or tumor seeding into the anterior chamber can be obtained by aqueous aspiration and Papanicolaou stain. Two limbal nodules of extrascleral extension from a ring melanoma were biopsied by Allaire et al[35] to confirm the diagnosis prior to enucleation. Fine-needle aspiration biopsy of iris ring melanoma was employed by Chaudhry et al[36] and by others of ciliary body and choroidal melanoma for cytologic diagnosis. Additional tests to be considered are fluorescein angiography, computed tomography (CT), magnetic resonance imaging (MRI),[53] and transillumination. The ^{32}P test has been used as a diagnostic adjuvant in the differentiation of benign from malignant choroidal lesions. This test is based on the principle that malignant tumor cells incorporate and use phosphorus to a greater degree than do normal tissues.[73] However, the ^{32}P test is not frequently employed because other methods such as ultrasonography, fluorescein angiography, ophthalmoscopy, and fine-needle aspiration biopsy are more accurate. Various authors have encouraged a thorough evaluation of intraocular masses especially those associated with glaucoma and opaque media. Unnecessary surgery, risking tumor dissemination, should be avoided.[53,73,74]

Retinoblastoma

The diagnosis of retinoblastoma is largely dependent on the clinical exam. Ultrasound, CT scan, MRI, and fluorescein angiography may be employed. Recently there has been little use of invasive techniques such as aqueous aspirates assessing lactic acid dehydrogenase levels to diagnose retinoblastoma.

Vitrectomy and fine-needle aspirates are also contraindicated due to the risk of tumor dissemination.[48]

Malignant Lymphoma and Leukemia

These tumors are largely diagnosed in the context of the systemic disease. Transocular fine-needle aspirate or vitreous biopsy with cytology may be helpful.

Medulloepithelioma

En bloc resection (by iridectomy or iridocyclectomy) will ultimately provide histologic diagnosis if the tumor is well localized. However, the clinician may utilize indirect ophthalmoscopy and slit-lamp biomicroscopy to facilitate the diagnosis. Most eyes with medulloepithelioma have been diagnosed and treated by enucleation with or without exenteration.[6,18,75]

Melanocytoma

Melanocytoma of the iris may be investigated through the techniques of transillumination (to exclude a cystic structure), ultrasonography (demonstrating the solid tumor with low internal reflectivity), fluorescein angiography (blocked fluoresence), high-frequency ultrasound biomicroscopy, fine-needle biopsy, or excisional biopsy.[8] Slit-lamp examination and gonioscopy are paramount; heterochromia and tumor necrosis may be present. Release of pigment from the necrotic melanocytoma stimulates an intense macrophagic response that infiltrates the trabecular meshwork. Although fine-needle aspiration biopsy may facilitate the diagnosis of intraocular tumors, Fineman et al[7] caution that fine-needle biopsy may not diagnose an occult focus of melanoma, and a negative cytologic diagnosis for malignancy does not rule out an intraocular malignancy. Therefore, they recommend local resection of an iris tumor as preferable to biopsy.

Juvenile Xanthogranuloma

Biopsy of other skin lesions demonstrating foamy histiocytes may assist in the diagnosis of juvenile xanthogranuloma of the iris.

Neurofibromatosis

Neurofibromatosis and François syndrome may be further diagnosed by CT and general physical examination looking for evidence of gigantism, café-au-lait spots, or neurofibromas. Lisch nodules of the iris are noted on slit-lamp examination more than 90% of the time.[76,77] Fluorescein angiography may further delineate the chorioretinal hamartomas; visual field testing, color vision evaluation, and CT or MRI may be useful in evaluating optic nerve gliomas. Ultimately in the evaluation of all tumors, enucleation with histologic staining and scanning electronmicroscopy may be employed for definitive diagnosis (Fig. 17–1).

Treatment and Management

How Is Glaucoma Associated with Intraocular Tumors Treated?

Iris Melanoma

A newly diagnosed iris melanoma is often managed by observation, and the glaucoma is conservatively managed with medical therapy. Slit-lamp photography and gonioscopy are essential to document growth of the lesion. Laser trabeculoplasty to the uninvolved meshwork can be performed if more aggressive treatment is required.[3] Shields and Proia[51] describe regression of neovascular glaucoma after excision of an iris melanoma. A diffuse or large iris melanoma may require enucleation. Filtration surgery is contraindicated due to the risk of dissemination or extrascleral extension.

Ciliary Body and Choroidal Melanoma

Uveal melanomas associated with glaucoma are typically large, diffuse, and associated with a poor prognosis. Therefore, enucleation is usually the standard of care. Intraoperatively, care must be taken to avoid iatrogenic elevation in the IOP, thereby risking tumor dissemination.[78–80] Several authors report that enucleation may decrease the patient's prognosis for survival. Within the group of patients with uveal melanoma, peak mortality occurs 2 years after enucleation and is associated with a 12% mortality rate. In contrast, nonenucleated patients exhibited a mortality rate of 1% per year of life. Contrasting these two melanoma patients groups, the mortality rate of the enucleated group equals that of the nontreated group at 7 to 8 years. Fraunfelder et al[81] have recommended the "no touch" technique during an enucleation to minimize the elevated IOP spike to 500 mm Hg, causing tumor cells to disseminate systemically and increasing the incidence of metastasis.[81]

Although glaucoma secondary to melanoma does not usually respond to medical treatment,[52] a trial of glaucoma medications is warranted. In rare cases, local excision or irradiation techniques may be employed. Ophthalmic oncologists may best perform radioactive plaque therapy. Surgical treatment with filtering surgery is contraindicated due to the risk of dissemination, extrascleral extension, or even metastases.[82] For intractable glaucoma that is medically uncontrollable, a cyclodestructive procedure or enucleation may be indicated for large melanomas. Kim et al[83] utilized helium ion irradiation predominantly to treat mostly large uveal melanomas. Patients with large melanomas who received higher radiation doses tended to develop neovascular glaucoma in contrast to patients who received low irradiation doses.

The Collaborative Ocular Melanoma Study (COMS) is an ongoing international study to evaluate small, medium, and large melanomas. Large melanoma is a potential metastatic tumor associated with patient mortality; this randomized study will evaluate the mortality rate of patients treated with enucleation alone versus external beam radiation and subsequent enucleation.[84] Prior to any surgical intervention, it is important to have the patient evaluated by a medical internist and to obtain some ancillary studies. These studies include a complete blood count, liver function studies, and chest x-ray. If the liver function studies

are abnormal, CT, MRI, or fine-needle liver biopsy may be necessary to evaluate the presence of metastatic disease. Following treatment of an intraocular melanoma, the patient should be periodically evaluated systemically for potential metastatic disease.

Metastatic Cancer and Leukemia

Treatment of metastatic cancer or leukemia with chemotherapy and possible local irradiation to the eye often results in resolution of the glaucoma. If the IOP remains elevated, the residual glaucoma can be treated medically, with cyclodestructive surgery or retrobulbar alcohol. Blind, painful eyes are enucleated. An incidental report describes washing necrotic tumor cells from the anterior chamber to treat glaucoma associated with leukemia.[56] Semiconductor diode laser transscleral cyclophotocoagulation was described by El-Harazi et al.[85] This case report described a patient with progressive infiltrative ductal carcinoma of the breast with metastasis to the brain, spine, liver, lung, and iris. This associated elevated IOP was refractory to maximal tolerated medications. The patient received contact transscleral semiconductor diode laser cyclophotocoagulation and subsequent external beam radiation; within 2 months the IOP was controlled, but the iris metastatic lesions did not resolve. In summary, diode laser has been used in refractory glaucoma but the risk of tumor dissemination is unknown.[85]

Retinoblastoma

Glaucoma associated with retinoblastoma usually occurs in the context of a unilateral advanced and large tumor. Therefore, enucleation is performed when a long section of optic nerve is obtained for histologic examination for metastatic or direct extention. In the presence of bilateral retinoblastoma, episcleral plaque radiotherapy or external beam irradiation may be an alternative in selected cases. Because preservation of useful vision is imperative, consultation with an ophthalmic oncologist is prudent. A detailed family history and exam under anesthesia (EUA) with funduscopy is important prior to enucleation. A lumbar puncture, bone marrow aspirate, and bone marrow biopsy should be obtained during the EUA to exclude metastases via cerebrospinal fluid and hematogenous extention. Additional ancillary studies may include a bone scan to identify distant metastases and a CT to document the presence of intraocular calcium and pinealoblastoma. Genetic evaluation and counseling are important to determine if the form of retinoblastoma is of hereditary nature. Because retinoblastoma is associated with a deletion of the second allele of the long arm of chromosome 13 (13q14), tumor suppressor gene product is not produced and these individuals are susceptible to secondary tumors such as osteosarcoma, malignant melanoma, chondrosarcoma, rhabdomyosarcoma, glioma, neuroblastoma, squamous cell carcinoma, and sebaceous cell carcinoma.[86–91]

Juvenile Xanthogranuloma

This is a benign and often self-limiting disease that responds to topical, subconjunctival, and systemic steroids. Rarely, external beam irradiation is

required. Trabeculectomy has not proven to be successful. Medical and not surgical treatment of the glaucoma should be attempted.[92–94]

Medulloepithelioma

Treatment of medulloepithelioma has not been standardized.[6] These frequently blind and painful eyes undergo enucleation. Small, well-circumscribed tumors may be locally resected by cyclectomy, iridocyclectomy, or iridocyclotrabeculectomy.

Melanocytoma

Melanocytoma treated with excisional biopsy may undergo normalization of the IOP.[23] Shields et al[23] described management of a case in this manner but caution that pigmented iris lesions associated with glaucoma may be difficult to differentiate from malignancy. Even benign tumors may undergo necrosis, and the decision to enucleate may be justifiable.

Sturge-Weber

The glaucoma associated with Sturge-Weber syndrome may initially be managed medically but frequently requires more definitive surgery later. Filtering surgery is associated with increased frequency of complications such as choroidal effusion or even expulsive choroidal hemorrhage. Some authors recommend preplaced sclerostomies or combined trabeculectomy/trabeculotomy to reduce the chance for complications.[95–97]

Neurofibromatosis

Neurofibromatosis associated glaucoma should be treated medically when possible, as the response to surgery is often poor.[98]

Future Considerations

Active research is being pursued in the treatment of retinoblastoma and choroidal melanoma in animal models and in limited human studies.

Murine models can be transgenically induced to produce retinoblastoma. Carney et al[99] have suggested that frequent subconjunctival carboplatin may be effective. The total dose of this drug appears to be important in tumor control in the murine transgenic retinoblastoma model. These data may also have significant clinical implications for the treatment of childhood retinoblastoma. Furthermore, Cicciarelli et al[100] studied the toxicity of subconjunctival injected carboplatin by monitoring the electroretinogram (ERG) and subsequent histologic changes in dwarf pigmented rabbits. This study suggests that subconjunctival carboplatin may be well tolerated in the treatment of retinoblastoma.

Stereotactic radiotherapy and radiosurgery may be beneficial in the treatment of uveal melanoma. Zehetmayer et al[101] utilized stereotactic Linac-based radiotherapy (linear accelerator) to irradiate uveal melanoma. This treatment may play a role in the conservative management of uveal melanoma. Mueller

et al[102] studied the efficacy of stereotactic radiosurgery of uveal melanoma with the Leksell gamma knife. Although only 25 patients were included in this short-term study, results indicate that radiosurgery using the Leksell gamma knife was beneficial in medium-size and large choroidal body melanomas that otherwise would be enucleated. These studies did not specifically discuss the issue of glaucoma associated with retinoblastoma or melanoma. However, these future medical and surgical modalities may facilitate visual acuity preservation and control of elevated IOP.

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◆ 18 ◆

Principles and Complications of Medical Therapy of Glaucoma

Rick E. Bendel and Mark S. Juzych

Definition

How are the Principles and Complications of Medical Therapy of Glaucoma Defined?

There are numerous recommendations on how to best use all of the available therapies for treating glaucoma patients. Such a proliferation of therapies indicates that no one pathway is best for any given patient, although now more than ever there are several good options. The six classes of drugs—miotics, beta-blockers, α-agonists, epinephrine derivatives, carbonic anhydrase inhibitors, and prostaglandin analogues—offer more than 20 different medications. Therefore, treatment must be tailored to each patient individually. (Tables 18–1 and 18–2 and Fig. 18–1).

This chapter offers an overview of the medications and their profiles, the importance of patient compliance, and how to optimize the lifelong treatment of glaucoma patients.

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Table 18–1. Available Antiglaucoma Agents

α-Adrenergic Blocking Agents

COSOPT (dorzolamide hydrochloride-timolol maleate ophthalmic solution)

Betagan Liquifilm (levobunolol hydrochloride)

Betimol 0.25%, 0.5% (timolol hemihydrate)

Ocupress ophthalmic solution, 1% sterile (carteolol hydrochloride)

OptiPranolol (metipranolol 0.3%) sterile ophthalmic solution (metipranolol hydrochloride)

TIMOPTIC 0.25% and 0.5% (timolol maleate ophthalmic solution) in OCUDOSE (dispenser)

TIMOPTIC 0.25% and 0.5% (timolol maleate ophthalmic solution)

TIMOPTIC-XE 0.25% and 0.5% (timolol maleate ophthalmic gel-forming solution)

Selective β-Adrenergics

Betoptic ophthalmic solution 0.5% (betaxolol hydrochloride)

Betoptic S ophthalmic suspension 0.25% (bextaxolol hydrochloride)

Carbonic Anhydrase Inhibitors

Azopt ophthalmic suspension 1% (brinzolamide)

COSOPT (dorzolamide hydrochloride-timolol maleate ophthalmic solution)

Daranide tablets (dichlorphenamide)

Diamox intravenous and tablets (acetazolamide)

Diamox sequel (acetazolamide)

Neptazane tablets (methazolamide)

TRUSOPT sterile ophthalmic solution 2% (dorzolamide hydrochloride ophthalmic solution)

Hypertonic Agents

OSMOGLYN oral osmotic agent (glycerin)

ISMOTIC (isosorbide)

Miotics

Humorsol sterile ophthalmic solution

Phospholine iodide ophthalmic solution (echothiophate iodide)

MIOSTAT intraocular solution (carbachol)

Ocusert Pilo-20 and Pilo-40 ocular therapeutic system (pilocarpine)

Pilopine HS ophthalmic gel (pilocarpine hydrochloride)

Pilocarpine ½%–10%

—Pilagan (pilocarpine nitrate)

—Pilocarpine hydrochloride

Carbachol 0.75%–3.0%

Prostaglandins

Xalatan sterile ophthalmic solution (latanoprost)

Sympathomimetics

Alphagan ophthalmic solution 0.2% (brimonidine tartrate)

EPIFRIN 1% sterile ophthalmic solution (epinephrine)

Iopidine 0.5% ophthalmic solution (apraclonidine hydrochloride)

IOPIDINE 1% sterile ophthalmic solution (apraclonidine hydrochloride)

PROPINE (dipivefrin hydrochloride)

Table 18–2. Available Classes of Glaucoma Medications, Their Contraindications, and Concurrent Systemic Agents to Avoid

Medical History	Medications
Beta-Blockers	
Respiratory problems	Systemic beta-blockers
Cardiac problems	Glycosides
Brittle diabetes	Ca^{2+} channel blocker, especially verapamil
Hyperthyroid	
Impotence	
Depression	
Raynaud syndrome	
? Hyperlipidemia	
Carbonic Anhydrase Inhibitors	
Respiratory acidosis	Aspirin
Hypokalemia	Diuretics
Sulfa allergy	Dilantin
Nephrolithiasis	Non steroidals
Incontinence	
Selective α-Adrenergic	
Renal failure	MAO inhibitors
Hepatic failure	Beta-blockers
Vascular disease	CNS depressants
Allergy	
Hypotension (brimonidine)	
Nonselective α-Adrenergic	
Cardiac disease	MAO inhibitors
Arrhythmia	Glycosides
Aphakia/pseudophakia	Beta-blockers
Hypertension	
Miotics	
Cataracts	Glycosides
Uveitis	Depolarizing agents (indirect agents)
Retinal detachment risk factors	
Occludable angles	
Bradycardia	
Prostaglandin Analogues	
Cystoid macular edema	None known
Uveitis	
Cosmesis, lash, iris, skin changes	

CNS, central nervous sytem; MAO, monoamine oxidase.

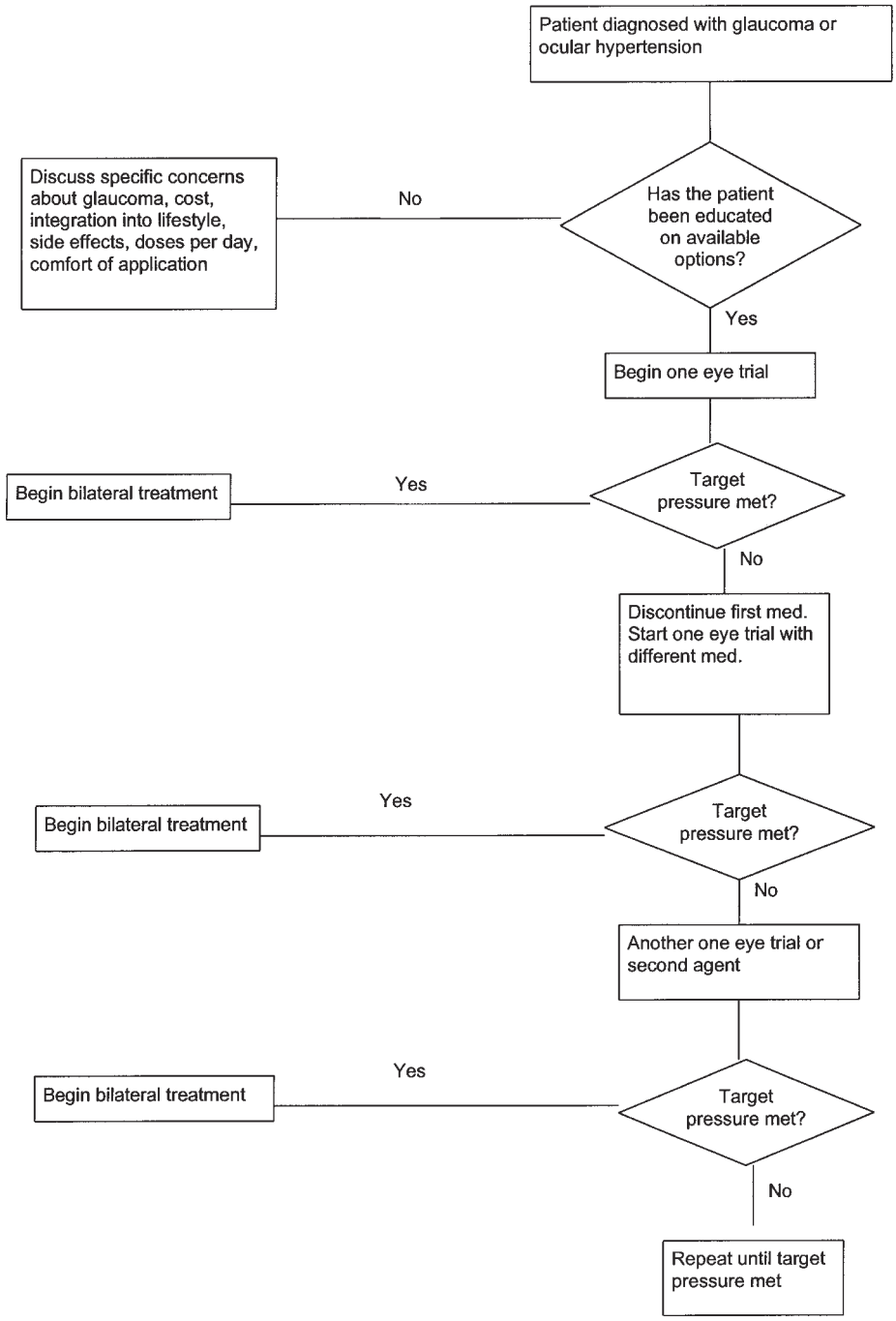

Figure 18–1. Medical management of patient with glaucoma or ocular hypertension.

Epidemiology and Importance

How Important Is Compliance?

Several studies have attributed a considerable amount of visual loss to noncompliance, which may make it a leading preventable cause of blindness from glaucoma.[1,2] One analysis in an urban setting indicated that 80% of visual loss in glaucoma occurred prior to presenting for diagnosis and treatment. Another 10% occurred as a result of noncompliance.[2] Improper compliance with nearly all types of medications seems to occur about 50% of the time.[3] Thus, a large proportion of the potentially preventable visual loss occurs as a result of noncompliance, which includes patients not filling prescriptions, as well as the improper use of medications, such as not taking them continually, discontinuing them prematurely, or taking them inappropriately. Compliance studies have consistently documented this problem. One population-based study found that administration errors precluded optimal response to therapy about 60% of the time.[4] The most significant errors in taking medications occur about 40% of the time due to failure to fill the medication prescription, not taking it continually, or stopping altogether.[4] The errors occurred due to a lack of patient comprehension, inadequate education, and improper prescription writing and labeling by physicians and pharmacists.

Diagnosis and Differential Diagnosis

Are Physicians Able to Judge the Compliance of Their Patients?

Most physicians assume that they have a fairly good idea about how well patients are complying by knowing them, interviewing them, and through experience. Studies have shown, however, that the doctor's judgment of patient compliance is about the same as chance. Some 30 to 50% of patients knowingly omit doses of their medications, but not all of them will admit it to their doctor. A study of chronically used medications demonstrated that doctors overestimated their patients' adherence to the regimen by about 50%, and patients' overstated their adherence by about 100%.[5] A study looking specifically at the compliance with topical pilocarpine using an electronic eye-drop monitor revealed a mean compliance rate of 76% [standard deviation (SD) = 24.3%].[6] Based on interview, the patients stated they had taken 97.1% (SD = 5.9%) of the prescribed doses, with the highest rate of actual compliance being the 24 hours prior to their return appointment. Clinician experience and patient demographics seemed to have little impact on these estimates. In fact, one study showed that the more senior a physician, the more likely he is to overestimate compliance.[7] A study in an ophthalmology residents' clinic for compliance with follow-up of patients found that many reasons exist for noncompliance, but the only modifiable step was to decrease the length of the wait in the doctor's office.[8] Noncompliant patients are more likely to be glaucoma suspects and not on any medications. Several reasons for dissatisfaction in study patients were present including insurance, transportation problems and fear—the only thing a doctor's office can modify is waiting time and efficiency of appointment. Eye care providers must accept that they may never really know what medications a patient is using.

Treatment and Management

How Can an Eye Care Provider Improve Patient Compliance?

Patients who understand their disease and have realistic expectations of their doctor and treatment regimen tend to be more compliant and have greater satisfaction with their health care.[3] Careful and frequent supervision is associated with better compliance. Psychological and emotional issues play a larger role in determining compliance than demographic factors. Regular contact with the doctor improves compliance, as does effective communication between the two.[9]

With the glaucoma patient, the physician should keep the treatment as minimal as possible. Each time a new medication is started, a one-eye trial should be performed. Each medication has about an 80% chance of succeeding in a given patient. Wide diurnal variations of pressure preclude starting a drop in both eyes, as one may mistakenly judge an intraocular pressure (IOP) decrease to be a successful trial when it is in fact only a diurnal variation. Eyes tend to vary their pressure in a symmetric manner, so if a drop is put in just one eye, the physician then has a frame of reference in the contralateral eye that has not had a treatment change.

The physician should instruct patients to instill eye drops at times each day when they have other routine things to do, such as eating meals or brushing teeth. Giving the patients two sets of drops, to keep at home and at work, may also be helpful. Schedules arranged by color-coding can help simplify a regimen that might otherwise be too confusing for a patient to follow. If the patient is unable to instill the drops, the help of family members should be enlisted or an instillation device used. A study determined that eye care providers can maximize compliance by instructing the patient how to instill the drops, observing the patient administering the drop, and using combination drops whenever possible.[10]

What Are the Possible Ways the Conjunctiva Can React to a Topical Medication?

The effects of medications on the conjunctiva are a concern for patient comfort and the potential success of filtration surgery in the future. Medications may cause cicatrizing conjunctivitis, allergic (acute or chronic) conjunctivitis, toxic conjunctivitis (pH, tonicity, contaminants), cumulative deposition as in adrenochrome deposits, microbial imbalance, nonspecific irritation, and other subclinical cellular and ultrastructural changes.[11]

What Should be Done to Help Patients Reduce Their Side Effects from Any of These Medications?

Nasolacrimal duct occlusion and eyelid closure are well-established ways to increase ocular absorption while decreasing absorption into the blood.[12,13] The ocular hypotensive effects of pilocarpine, timolol, and carbachol were increased by nasolacrimal occlusion, allowing half the concentration to be used as well as less frequent application.[13] At the very least, patients should close their eyes for 1 minute after the drop is instilled. The most optimal application

of drops would be nasolacrimal duct occlusion combined with eyelid closure for 5 minutes, but most patients find it difficult to sustain eyelid closure for 5 minutes, so 3 minutes is a good compromise. Patients taking timolol reduced serum levels by 65% with eyelid closure and 67% with nasolacrimal duct occlusion.[14] Another study showed that nasolacrimal duct occlusion reduced blood levels of timolol by 71%.[12] Fluorescein concentration was increased by 69% in the anterior chamber by nasolacrimal duct occlusion, and lid closure alone increased it by 46%, indicating that these methods increase the concentration of the medication in the eye while decreasing the amount of drug delivered to the nasal mucosa.[14]

How Do Beta-Blockers Lower IOP?

β-Adrenergic antagonists reduce the production of aqueous humor. β-Adrenergic receptors have been found on the iris, ciliary body, and trabecular meshwork. A plausible theory on the mechanism of action is that beta-blockade reduces the adenylyl cyclase activity, which reduces aqueous production.[15]

What Are the Differences Between the Beta-Blockers?

The nonselective beta-blockers are timolol maleate, timolol hemihydrate, carteolol, levobunolol, and metipranolol. Timolol maleate is also available in a solution that forms a gel in the eye after applying. The gel maintains the medication in contact with the eye for a longer period of time and may increase efficacy and lower side effects.[16] However, a study comparing the systemic effects of once daily timolol hemihydrate and timolol gel-forming solution demonstrated that there was no significant difference in IOP reduction or in systemic beta-blockade between the two medications.[17] Levobunolol has the longest half-life. Metipranolol is similarly effective, although clinicians need to be aware of the reports of granulomatous uveitis in patients treated with this drug.[18,19] Carteolol may have some different pharmacologic features from the other beta-blocker because of its intrinsic sympathomimetic activity, although clinical studies have not yet demonstrated this.[20]

Betaxolol is cardioselective by minimizing β_2-inhibition. Betaxolol 0.5% stings when applied, so a 0.25% suspension was developed for comfort, and it is equally efficacious.[21] The suspension is thought to slow the delivery and enable a lower concentration to be used, lessening the local irritation produced by a bolus delivery of betaxolol. Most studies have found betaxolol to be less effective than timolol and levobunolol.[22,23] Timolol 0.5% lowered IOP an average of 29% compared to 26% for betaxolol 0.5%; levobunolol lowered the IOP by 6.2 mm Hg compared to 3.7 mm Hg for betaxolol 0.5% in patients with an average baseline IOP of 25 mm Hg. Betaxolol is safer to use in patients with pulmonary disease, although it may still provoke asthma.[24]

Daily cost of β-adrenergic therapy should also be a consideration. A comparison of drop size, cost, and wasted medication found that generic timolol maleate and Betimol were the least expensive, at 55 and 57 cents per drop, respectively. Betoptic-S and Betagan were the most costly, at $1.60 and $1.35, respectively. Timoptic$_{xe}$ had the largest drop volume (49 μL), whereas Ocupress (31 μL) had the smallest.[25]

What Are the Side Effects of Beta-Blockers?

Ocular side effects can include punctuate keratopathy, dry eyes, allergic blepharoconjunctivitis, nonrefractive visual disturbances, and occasionally corneal anesthesia.[26,27] A study comparing betaxolol 0.5% and timolol 0.5% demonstrated that some corneas will develop a long-lasting corneal anesthesia after use of the drops, which can predispose a patient to more serious corneal complications, such as keratitis. This is more likely to occur in patients who are older than 70. The authors recommended performing periodic aesthesiometry to identify these patients.[27]

All of the beta-blockers may cause or worsen congestive heart failure, asthma, chronic obstructive pulmonary disease, depression, ankle edema, disturbed sleep, weakness, dermatologic and gastrointestinal problems, bradycardia, memory problems, impotence, hyperlipoproteinemia, and confusion, and may worsen Raynaud's syndrome and myasthenia gravis.[26-29]

What Are Important Interactions Between Beta-Blockers and Calcium Channel Blockers?

Increased risk of lower blood pressure, bradycardia, atrioventricular (A-V) block, and even asystole are considerations for patients combining these medications. Verapamil is of special concern as cases of complete heart block, A-V nodal delay and sinus node dysfunction have been reported when timolol was used in combination with this calcium channel blocker.[30,31] If a calcium antagonist needs to be used concomitantly with beta-blocker therapy for glaucoma, one should be used that has little effect on heart rate or conduction.

What About the Use of Topical Beta-Blockers and Diuretics?

Increased risk of systemic hypotension and the use of both drugs can increase hypolipoproteinemia. Thiazide diuretics are more likely to increase blood sugar and triglyceride levels.[32]

What About the Use of Topical Beta-Blockers and Cardiac Glycosides?

Most commonly, bradycardia may be potentiated. The risk of A-V dissociation is increased, and there are case reports of cardiac arrest.[32] Xanthopsia is usually a symptom of digitalis toxicity, and with glaucoma medications it may also present as decreased visual acuity without xanthopsia.[33]

What About the Use of Topical Beta-Blockers and Angiotensin-Converting Enzyme Inhibitors?

These drugs are relatively safe to use together as long as the increased risk of systemic hypotension is addressed.

What Happens When Systemic and Topical Beta-Blockers Are Used at the Same Time?

All of the side effects of the topical beta-blockers may be exacerbated. It is important to remember that systemic administration of beta-blockers lowers IOP, and that topical administration is often less efficacious when these agents are taken orally.[34] Special consideration must always be given to the cardiopulmonary status of any patient on topical and systemic beta-blockers concomitantly.

What About the Effects of Beta-Blockers on Blood Lipid Profiles?

Nonselective beta-blockers have been shown to unfavorably affect the lipid profile by reducing high-density lipoprotein (HDL) levels and increasing triglycerides[35]; at present there is no evidence to indicate that these changes affect the clinical outcome of the patient. Carteolol may have a slight advantage over other beta-blockers in that one study demonstrated a 3.3% reduction of HDL compared to an 8% reduction with timolol.[35] The 58 healthy males in this study also showed a 4.0% increase in the total cholesterol (TC) to HDL ratio while taking carteolol, and a 10.0% increase in this ratio while on timolol 0.5%. The drugs were taken twice a day with no nasolacrimal duct occlusion. A recent 12-week study compared timolol 0.5% twice daily to carteolol 1% twice daily in women over 60 with open-angle glaucoma or ocular hypertension. The investigators found no change in HDL and TC/HDL while the patients were on carteolol, but found a decrease of HDL and an adverse effect on TC/HDL while the patients were on timolol.[17] This may be due to the intrinsic sympathomimetic activity of carteolol. Although the studies are still considered preliminary, some ophthalmologists prefer carteolol to other beta-blockers in patients with unfavorable lipid profiles.

What About Patients Being Treated for Diabetes?

Adult-onset diabetes is an important risk factor in treating glaucoma. With multiple medical regimens for a patient to follow, compliance will become even more difficult, increasing the likelihood of complications. One of the most important complications of diabetic treatment is hypoglycemia. Beta-blockers can blunt or mask the symptoms of hypoglycemia, lower blood sugar, and delay recovery.[32]

Are There Other Systemic Medications to Keep in Mind When Treating a Patient with a Topical Beta-Blocker?

Hormonal replacement therapy in women may increase headache when used with a beta-blocker. Some beta-blockers have shown increased effect when used concomitantly.[16] Aspirin and nonsteroidal antiinflammatory drugs can decrease the effect of beta-blockers. A patient treated with thyroid hormonal supplementation and converted to an euthyroid state may have a reduced effect of the beta-blocker.

How Do Carbonic Anhydrase Inhibitors Work?

They primarily work to decrease aqueous humor production by inhibiting the formation of bicarbonate in the ciliary processes, which is linked to sodium secretion to form aqueous. Systemic acidosis decreases aqueous formation, and although oral carbonic anhydrase inhibitors create a metabolic acidosis, it is unclear what amount of reduction in aqueous production this may cause.[36]

What Are the Different Carbonic Anhydrase Inhibitors Available?

Oral and topical carbonic anhydrase inhibitors are used to treat glaucoma. The oral agents that have been used in the chronic treatment of glaucoma include acetazolamide, methazolamide, ethoxzolamide (no longer available), and dichlorphenamide. Topical agents include dorzolamide and brinzolamide.

Acetazolamide is available in tablets, and is generally taken in doses of 125 to 250 mg four times a day. A twice-a-day slow-release capsule (Diamox Sequel 500 mg) is available. Methazolamide is available in 25- and 50-mg 50-tablets and administration is two or three times a day, up to 100 mg three times a day. Its half-life is 14 hours compared to 5 hours for acetazolamide. It produces less metabolic acidosis and fewer side effects compared to acetazolamide tablets, but is slightly less efficacious.[37] One study showed a greater tolerance for Sequel compared to methazolamide.[38] Dichlorphenamide has similar or perhaps greater efficacy at 25 to 50 mg up to three times a day, but is less well tolerated.[38] The investigators in this study questioned whether maximal efficacy is associated with more severe side effects, which may indicate more extensive biochemical alterations from the medication.

Dorzolamide 2% was the first topical agent available, with brinzolamide 1% recently becoming available (used two to three times a day).

How Well Do the Topical Carbonic Anhydrase Inhibitors Work Compared to Timolol?

Dorzolamide 2% three times a day reduced the IOP by 22% at peak and 18% at trough.[39] A 12-month double-masked study comparing timolol maleate 0.5% and betaxolol 0.5% twice daily and dorzolamide 2% three times daily found that peak IOP reduction measured 2 hours after instillation was not statistically different between the three medications.[40] The trough IOP at 5 and 8 hours after instillation revealed that timolol's IOP reduction was significantly better than betaxolol and brinzolamide, although the trough IOPs of the latter two were not significantly different from one another. Brinzolamide 1% administered twice and three times daily was compared to dorzolamide 2.0% three times daily and timolol maleate 0.5% twice daily.[41] In both dosing regimens brinzolamide was statistically equivalent to dorzolamide thrice daily, although neither of the drugs was as effective as timolol.

How Well Does Dorzolamide Work with Timolol, Now that the New Timolol/Dorzolamide Combination Drop has Become Available?

Aqueous flow reduction was found to be 18% for dorzolamide alone and 47% for timolol alone, and that the two used together were nearly completely additive at 55%.[42] Note that in this study the aqueous inhibitory affect of timolol was 2.6 times as great as dorzolamide. The Dorzolamide Timolol Study found that the combination drop was comparable to timolol 0.5% twice a day and dorzolamide 2.0% three times in efficacy and tolerability.[43] The study did find that the group of patients taking the timolol 0.5% twice a day and dorzolamide 2.0% three times a day had a slightly lower IOP in the early morning and the greatest IOP difference at hour 8, which was 2 hours after the midday dose of dorzolamide. The slightly lower IOP in the morning and afternoon are small and not thought to be significant. Other studies have shown that dorzolamide is additive to other aqueous suppressants that have been in previous long-term use by patients prior to instituting treatment with dorzolamide.[44]

Are Topical Agents as Effective as Oral Agents?

From anecdotal evidence, many physicians have felt that the topical agents are not as effective as oral agents, and the answers in the literature are still not clear. Some studies have shown that the agents are equally effective. Eyes treated with dorzolamide 2.0% three times a day were compared to those treated with acetazolamide 250 mg four times a day and were found to have similar reductions in aqueous humor formation and IOP.[45] Also, the previous study did not demonstrate a further reduction in IOP when dorzolamide was added to patients on acetazolamide and vice versa, concluding that they are not addictive. A different study has demonstrated that dorzolamide reduced aqueous production by 17%, whereas acetazolamide reduced it by 30%. Adding acetazolamide to dorzolamide-treated eyes reduced aqueous production by an additional 16%.[46] A single dose of dorzolamide was found to have a comparable high efficacy to a single dose of acetazolamide 125 mg in preventing pressure spikes following yttrium-aluminum-garnet (YAG) posterior capsulotomy.[47] Other studies have shown that there is not a significant benefit when adding acetazolamide to an eye already treated with topical carbonic anhydrase inhibitors, and they are equally efficacious in eyes already on maximal medical therapy.[48]

Does Dorzolamide Have Any Influence on Visual Function?

Normal-tension glaucoma patients placed on dorzolamide had improved contrast sensitivity after 2 to 4 weeks of treatment compared to controls who received placebo.[49] Patients were also found to have accelerated arteriovenous passage time, but no change in blood flow in retrobulbar vessels.

How Does Dorzolamide Compare to the More Recently Released Brinzolamide?

Brinzolamide 1% twice daily and brinzolamide 1% three times daily were found to be equally efficacious to one another and to dorzolamide three times daily.[41] Ocular complaints were significantly less with brinzolamide, with only 2 to 3% complaining of ocular discomfort compared to 16.4% taking dorzolamide.[41] Brinzolamide has a more physiologic pH, requiring it to be delivered as a suspension, compared to dorzolamide, which is more acidic but is delivered as a solution.

What Are the Side Effects of Carbonic Anhydrase Inhibitors?

Fortunately, the most common side effects are the most benign, albeit annoying. Most patients experience transient paresthesias, urinary frequency, and a metallic taste. Other annoying side effects, such as diarrhea, fatigue, malaise, nausea, renal colic, decreased libido, abdominal pain, and depression, may continue throughout the course of treatment. More serious side effects include renal stone formation, hirsutism, and the most rare but dreaded bone marrow suppression.[32] Serious and near-fatal complications such as Stevens-Johnson syndrome can occur after even one dose of an oral carbonic anhydrase inhibitor, such as after a cataract surgery or laser procedure when a single dose may be given, even when no sulfa allergy is present.[50] The agents all include a sulfonamide group on their ring structure, so sulfa allergy is a contraindication. All of these side effects are much less common, but possible, with topically applied carbonic anhydrase inhibitors. During clinical trials with dorzolamide, urinary and hematologic tests were routinely performed and did not find any disturbances.[51] This study suggests that the systemic inhibition of carbonic anhydrase is insufficient to produce biochemical adverse effects. Five percent of patients discontinue topical carbonic anhydrase inhibitors due to adverse reactions, most of which are ocular.

Many systemic drug interactions occur with carbonic anhydrase inhibitors and some important interactions to keep in mind are described below.

What Are Some Concerns When a Patient on Carbonic Anhydrase Inhibitors Is Being Treated with Calcium Channel Blockers?

The side effects of nausea and/or vomiting and malaise may become worse. Both of these drugs can cause paresthesias.

Is Concomitant Use of Carbonic Anhydrase Inhibitors and Diuretics a Special Concern?

Both drugs can lead to hypokalemia, which makes the adverse effects of carbonic anhydrase inhibitors worse and also causes a greater chance of toxicity from cardiac glycosides.[32] The chance of developing agranulocytosis is greater when they are used together.

What About Carbonic Anydrase Inhibitors Used with Angiotensin-Converting Enzyme Inhibitors?

Both drugs can lead to bone marrow suppression.

How About Carbonic Anhydrase Inhibitors Used Concurrently with Systemic Beta-Blockers?

They are relatively safe to use together, but both can cause insomnia, dizziness, depression, and nausea/vomiting.

What Are the Special Considerations About Concomitant Use of Carbonic Anhydrase Inhibitors and Aspirin?

Both drugs can lead to metabolic acidosis and can also cause hypokalemia. There are reports of carbonic anhydrase inhibitor accumulation in the central nervous system and subsequent depression when salicylates were used together.[32]

Other nonsteroidal antiinflammatory drugs may decrease the efficacy of carbonic anhydrase inhibitors, and both may lead to bone marrow suppression.

How About Patients Who Are Being Treated for Diabetes with Hypoglycemics?

Carbonic anhydrase inhibitors can increase blood glucose levels. Elevated blood sugars are more poorly tolerated with lowered levels of potassium.

What Are Some Other Common Medications that Can Interact with Carbonic Anhydrase Inhibitors?

Headaches may become worse in patients on hormonal replacement. Patients on thyroid replacement may have a lower uptake of iodine by the thyroid gland. Acetazolamide has been shown to cause a significant increase in the blood levels of cyclosporine.[52] Cyclosporine blood levels that have been in the safe therapeutic range have been shown to increase five times when acetazolamide is given, which enhances the likelihood of toxicity.

What Are the Different Types of Miotics?

The direct-acting agents are acetylcholine chloride and pilocarpine. Indirect-acting agents are anticholinesterases, including echothiophate iodide, demecarium bromide, and diisopropyl fluorophosphate. Carbachol has both direct- and indirect-acting mechanisms.

How Do Miotics Work?

Direct-acting agents stimulate the parasympathetic muscarinic receptor site, resulting in contraction of the longitudinal muscle of the ciliary body attached to

the scleral spur, which in turn results in improved aqueous outflow through the trabecular meshwork.[53,54] Indirect-acting agents inactivate acetylcholinesterases. The reversible agent demecarium inactivates acetylcholinesterase by binding to it, and the action may be reversed by slow hydrolysis. The irreversible agents bind by alkyl phosphorylation to the enzyme, resulting in its inactivation. The end result is accumulation of acetylcholine at the muscarinic receptors, increasing their degree of stimulation. Pilocarpine is generally used four times daily, carbachol three times daily, and the indirect agents once or twice daily. The frequent dosing of the pilocarpine is difficult for most patients; a weekly Ocusert delivery system is available, and a slow-release 4% pilocarpine gel administered at bedtime is also available. The other advantage of Ocusert is that the pilocarpine base is free of preservatives.

Side effects occur with the use of miotics, and a few systemic medication considerations are important to keep in mind. These adverse effects are reviewed below.

What Are the Side Effects of Miotics?

Ocular side effects are quite common. Patients usually experience a temporal and/or supraorbital headache as the medication activates the ciliary muscle, but over a short period of time this resolves. The pupillary miosis results in reduced vision in lower illumination and considerable difficulty in patients with central lens opacities. Accommodative myopia is induced which is greater in younger patients, minimal in patients over 60, and nonexistent in pseudophakes. Retinal detachment may occur, shallowing of the lens/iris diaphragm may induce acute- or chronic-angle closure, and iris cysts may develop.[55,56] Although the etiology and causality of retinal detachments are not proven, conservative recommendations before starting a patient on miotics include a 360-degree retinal exam and pretreatment of chorioretinal disease. Then it is recommended to start with the lowest dose, time-released delivery when possible, and patient education should be provided.[55] Although time-released pilocarpine is considered safer, it has also been associated with retinal detachments.[56] Cataracts may be exacerbated or formed with the use of these agents; they are dose related and will continue to develop after cessation of therapy.[57] Patients over the age of 60 appear more vulnerable to this effect, although a 13-year-old girl developed lens opacities after the use miotics for treating esotropia.[58] Increased permeability of the blood–aqueous barrier occurs, which is of concern when these patients undergo intraocular surgery. Increased conjunctival fibrosis and cicatricial pemphigoid have also been reported.[11] All of the above-mentioned side effects can occur with all of the miotics, but are more prevalent with the stronger indirect-acting miotics.

Patients with angle recession have experienced IOP increases after being placed on miotics. These patients probably rely more on uveoscleral outflow, which the miotics decrease.[59] The authors tested this theory, and found that the rare patient with an IOP increase on miotics may experience a therapeutic IOP decrease on mydriatics.

Systemic side effects include nausea and/or vomiting, slowing of the heart, sweating, pulmonary edema, diarrhea, and bronchospasm. The activation of the muscarinic receptors on these organs causes these side effects. Corneal

absorption is variable with these drops, and it is advantageous to have them instilled after other topical drops to facilitate uptake.

Can Miotics Be Dangerous to Patients Who Receive Anesthesia?

Cholinesterase inhibitors may result in prolonged respiratory depression in patients receiving succinylcholine during general anesthesia.[32] The agents inhibit endogenous cholinesterase, which means that the body will be unable to inactivate succinylcholine, giving it a dramatically prolonged effect.

What Type of Interactions Can Occur with Concomitant Use of Miotics and Angiotensin-Converting Enzyme Inhibitors and/or Calcium Channel Blockers?

Headache may be worsened, vasodilatation may be increased, and hypotension may result.

What Can Systemic Beta-Blockers Do While a Patient Is on Miotics?

Bronchoconstriction may be aggravated in patients with asthmatic tendencies. Beta-blockers may increase the risk of nausea and vomiting or may result in lower blood pressure.

Thyroid supplementation may increase tremor, muscle weakness, and diarrhea. Nonsteroidals, aspirin, and hormonal replacement can exacerbate headache and the chance for nausea and/or vomiting.

What Are the Different Types of α-Adrenergic Agonists?

The major subtypes used in the treatment of glaucoma are selective and nonselective agonists. The nonselective agonists include epinephrine and dipivefrin. The selective agonists include apraclonidine and brimonidine.

How Do Nonselective α-Adrenergic Agonists Work?

Nonselective agents have both α- and β-adrenergic activity. A complex mechanism involving the autonomic nervous system and receptors in the eye results in reduction of IOP. α-Adrenergic activity decreases aqueous production, whereas β-adrenergic activity increases it[60] and probably increases conventional and uveoscleral outflow.[34]

How Do Selective α-Adrenergic Agonists Work?

Apraclonidine lowers IOP by decreasing aqueous humor formation. Although it does not alter outflow, it may decrease episcleral venous pressure.

Brimonidine decreases aqueous production and may also increase uveoscleral outflow.

What Are the Side Effects of the Nonselective α-Adrenergic Agonists?

Initial vasoconstriction followed by vasodilatation can result in hyperemia, which is not clinically significant but may be cosmetically annoying to the patient. Tearing and irritation are also quite common, with occasional episodes of brow ache and even corneal edema. Mydriasis may result in photophobia, which may be enhanced by the use of beta-blockers and may precipitate angle closure. Allergic blepharoconjunctivitis may result after long-term use in about 10 to 15% of patients,[61] and adrenochrome deposits have long been known to develop.[32] They cause a breakdown of the blood–aqueous barrier, and 10 to 20% of aphakic patients may develop cystoid macular edema.[62,63] The incidence is probably much greater as only more significant visual loss seems to be noticed; visual loss in people who were formerly 20/20 and have dropped to only 20/30 or 20/40 may go unnoticed.[62] Angiographically, the macular edema was found to be completely reversible with cessation of its use.[63]

Systemic side effects include tachycardia, arrhythmias, extrasystoles, hypertension and headache.[61] These agents should probably be avoided in patients with hyperthyroidism or cardiac disease and in patients being treated for depression with monoamine oxidase inhibitors and tricyclics.

What Are the Advantages of the Prodrug Dipivefrin?

Its concentration is one-twentieth that of epinephrine, and as a result cardiovascular and systemic side effects are not clinically significant; furthermore, it must be activated by corneal esterases. Its local side effects are less, except that long-term use often results in a follicular conjunctivitis and hyperemia, but no adrenochrome deposits.[64] Cystoid macular edema seems to occur less frequently with dipivefrin than with epinephrine, although the incidence would be expected to be similar since its efficacy is based on the intraocular concentration of epinephrine.[65]

What Are the Side Effects of Selective α-Adrenergic Agonists?

Ocular effects include lid retraction, conjunctival blanching and subsequent redilatation. The most annoying and common problems that occur in 10 to 50% of patients are allergic blepharoconjunctivitis and dermatitis.[66] They are much more common and severe with apraclonidine, which is infrequently used today since brimonidine became available. The allergy occurs in 10 to 15% of patients on brimonidine after 3 to 9 months of treatment.

Systemic side effects are most commonly dry mouth and/or nose. The advantage of apraclonidine is that it does not easily cross the blood–brain barrier, lessening the chance of centrally mediated effects, which include inhibited

central sympathetic activity resulting in fatigue, drowsiness, and hypotension.[66] Brimonidine is more lipophilic and thus crosses the blood–brain barrier more easily and may cause these side effects.[67]

What Are Some Possible Effects Nonsteroidal Drugs or Aspirin May Have When Used with α-Adrenergics?

Both of these agents can decrease the IOP-lowering effect of the adrenergics. Sometimes when they are used together they may increase blood pressure.[32]

Are There Interactions with Angiotensin-Converting Enzyme Inhibitors?

α-Adrenergics may decrease their efficacy.

What About Calcium Channel Blockers and Diuretics?

Both drugs may increase the possibility of nausea/vomiting, diarrhea, and abdominal pain. Diuretics may also increase the chances of palpitations and headache.

Are There Any Concerns in Diabetics or Patients on Thyroid Supplements?

The α-adrenergics can stimulate hyperglycemia and decrease the effect of insulin. Thyroxin can increase the efficacy of adrenergics and make a patient more susceptible to a pressor response.

What Are the Available Prostaglandins?

Presently, in the United States, latanoprost 0.005% is the only available agent. Unoprostone is under investigation here and is becoming widely used in Japan and Latin America, and it seems to have fewer local ocular side effects in preliminary studies.[68,69]

What Are the Side Effects of Latanoprost?

The most common and disturbing side effect to patients and practitioners is the deepening of the iris color. It is much more common, up to 20 to 30%, in mixed-color irides compared to solid-color irides.[70] A case report indicated that after 5 months of treatment a 13-month-old infant developed increased pigmentation with blue-gray eyes.[71] Patients may experience conjunctival hyperemia when instilling latanoprost and possibly cystoid macular edema. Another side effect has become better known with unilateral use of the medication—thickening and lengthening of lashes.[72] An investigator found an average of 19.5% increase in lash length, increased number of lashes, more abundant vellus hairs in the lateral canthal area, hyperpigmentation of the lashes, and increased curl-

ing. The effect is more prominent with more darkly pigmented hair. One of the first case reports of lash changes demonstrated that the changes became obvious at 14 weeks in a single-treated eye, and 8 weeks after latanoprost 0.005% was added to the contralateral eye the lashes appeared the same in both eyes.[73]

Systemic side effects are limited due to the low concentration and short half-life in the blood. The multicenter trials did not reveal any serious systemic side effects, but some patients do experience a flu-like syndrome, upper respiratory symptoms, and headache.[32] The study involving 277 patients for 24 months in the United Kingdom did not reveal any systemic side effects.[74]

What Is Known About Latanoprost and Cystoid Macular Edema?

There are case reports of possible cystoid macular edema, but the causality is not clear.[75] In general, these cases have occurred in eyes with a past history of retinal disease and aphakia. A recent study demonstrated increased blood aqueous disruption and an increased incidence of angiographically documented cystoid macular edema in early postoperative pseudophakes, and that aqueous flare was increased over the eyes of patients not taking latanoprost 0.005%. The aqueous flare difference was not present on the first postoperative day but rather at 3 days and 2 weeks, suggesting that latanoprost enhances the production of inflammatory mediators. However, the concurrent use of topical nonsteroidals significantly prevented these side effects while not decreasing the IOP lowering effect of latanoprost.[76]

Does the Time of Instillation Matter?

The clinical trials of the drug had protocols with a standardized application at 8:00 P.M. No evidence clearly indicates that the time of instillation affects the drug's efficacy. Latanoprost was felt to be more effective when used at night because of the results of the Scandinavian arm of the clinical trials. Scandinavian patients were found to have significantly greater IOP reduction when latanoprost 0.005% was instilled in the evening compared to the morning.[77] This has not been produced in any other studies and may have been caused by a difference in study design or patient population. Around-the-clock efficacy has been well demonstrated by a study instilling latanoprost 0.005% in the morning and monitoring IOP around the clock.[78] The results demonstrated equally efficacious IOP reduction during the day and during the night.

How Does the Efficacy of Latanoprost Compare to that of Timolol?

Studies routinely use timolol as the standard against which other drugs are compared. Latanoprost is the only drug that has shown around-the-clock better control than timolol.[70] One study has shown that latanoprost offers a significantly lower IOP than timolol, and when patients were switched to latanoprost a significantly greater IOP reduction was obtained.[78] Patients who

had been treated with timolol 0.5% twice daily for 1 year were switched to latanoprost 0.005% once a day, and showed an additional 8% IOP reduction.

Does Latanoprost Work with Miotics?

Logically these two medications would seem to be antagonistic because miotics decrease uveoscleral outflow by contracting the ciliary muscle, and the mechanism of action of latanoprost is to increase uveoscleral outflow. Uveoscleral outflow is theorized to occur through the interstitial spaces of the ciliary muscle, which are decreased by cholinergic agonists.[79,80] A study using supramaximal dosages of physostigmine in conjunction with latanoprost found the effects to be mostly additive, although the maximal effect was less than in previous studies where latanoprost 0.005% was the only eye medication.[81] Eyes suboptimally controlled on maximum tolerated medications demonstrated significantly lower IOP when latanoprost was added, and any strength of pilocarpine did not have a significant effect on its efficacy.[82] The only factors in this study found to decrease its efficacy were a starting IOP of greater than 24 mm Hg and more than two previous incisional glaucoma surgeries.

How Well Does Latanoprost Work with Topical Carbonic Anhydrase Inhibitors?

Fluorophotometry revealed that latanoprost had no effect on the aqueous suppression of dorzolamide and that the two agents were additive.[44,83] Aqueous humor was suppressed 13% by dorzolamide 2%, and no suppression was found with latanoprost 0.005%. The two drugs are additive but do not enhance the activity of the second drug. The authors recommend that both drugs be tried separately and then added together to see if the effect of the agents used together is superior to either drug used alone.[83]

Are There Drug Interactions?

No significant drug interactions have yet been reported.

What Is the Role of Hyperosmotic Agents in the Treatment of Glaucoma?

The hyperosmotic agents are used as a short-term or emergency treatment of glaucoma, such as acute angle-closure glaucoma, preparation for intraocular surgery, and with other acute IOP elevations.

What Are the Available Hyperosmotic Agents?

Intravenous agents include urea, mannitol, ascorbic acid, and sorbitol and glycerol solutions. Oral agents include isosorbide, glycerol, and ethyl alcohol. The oral agents are slightly less effective and take effect a little more slowly than the intravenous agents.[84]

Isosorbide is not metabolized like glycerol and is used preferentially in diabetics and to avoid caloric intake. Mannitol and intravenous glycerol may be preferred in inflammatory and neovascular glaucomas due to their decreased tendency to penetrate the eye.

What Are the Side Effects of the Hyperosmotic Agents?

Common side effects are diuresis, headache, and back pain, and the oral agents also commonly cause nausea and vomiting.[85] The agents may cause severe side effects of volume and electrolyte derangements in patients with cardiac, pulmonary, or renal deficiencies, such as congestive heart failure and hyponatremia.[32,86] Acute renal failure has also been reported in patients with previously normal renal function.[87] Subdural hemorrhage has also occurred and is theorized to be a result of cortical shrinkage from dehydration, causing fragile veins to rupture.[88]

How Do the Hyperosmotic Agents Work?

The agents increase the serum osmolality and draw water from the eye, primarily from the vitreous.[89] The IOP-lowering effect is greater the higher the IOP, and a relatively minor effect is seen in an eye with a normal IOP.[90] A rebound increase in IOP is possible when the serum/vitreous gradient may reverse as a result of a lower serum osmolality following significant diuresis.

In Which Settings Are the Hyperosmotics Most Effective?

They are particularly useful for acute angle closure. Not only do they lower the IOP rapidly, but due to vitreous shrinkage they also deepen the anterior chamber.[84] The reduction of vitreous hydration is also particularly useful in ciliary block glaucoma.[91] Transient and dramatic IOP increase after trauma and hyphema may also be quite responsive.[92] Finally, many surgeons feel that preoperative administration lowers some surgical risks during intraocular surgery, but it is not clear if there is any benefit with smaller-incision cataract surgery.

What About Using Marijuana for Glaucoma?

Interest in cannabinoids started in the 1970s when miotics, epinephrine, and oral carbonic anhydrase inhibitors were the only medications available.[93] Smoking marijuana reduces IOP in about 65% of people by about 20 to 25%.[94,95] Topical application has not proven effective in humans. The mechanism of its action is unclear, and it may be an epiphenomenon associated with the euphoria and relaxation; only patients who experienced a "high" had significant IOP reduction.[93] Another study showed that the IOP reduction followed a decrease in blood pressure, suggesting that the mechanism may be decreased perfusion to the ciliary body.[95]

What Are the Side Effects of Marijuana, Inhaled or Ingested?

Ocular side effects include hyperemia, decreased lacrimation, nystagmus, blepharospasm, and photophobia. Systemic side effects of smoking marijuana include hypotension, euphoria, conjunctival hyperemia, tachycardia, and alter-

ation of mental status. Long-term side effects are at least emphysematous changes to the lungs and possibly changes in the hormonal system and brain.[96] In a disease that requires 24-hour control and a lifetime commitment to treatment, these side effects are unacceptable. Additionally, smoking marijuana lowers IOP for only 3 to 4 hours, and control would require frequent administration. About 3,000 marijuana cigarettes would need to be smoked each year.[94] In spite of these drawbacks, a recent review of the medicinal uses of marijuana has stated that further research needs to be done on its potential uses to treat glaucoma, and that there may be some settings where its use may be helpful.[97]

How May Cannabinoids Become a Part of Glaucoma Regimens in the Future?

Cannabinoid analogues are being developed that are capable of reducing IOP without the side effects of marijuana.[98] Newer topical delivery systems and oral formulations that lack the psychoactive aspects or marijuana may make routine use of this class of drugs more feasible.[94] Further research may develop this class as a new and useful medication to treat some glaucoma patients.

What Is The Best Way to Decide on and Begin Treatment?

Figure 18–1 is a simple methodical paradigm that facilitates successful, simple, and effective glaucoma treatment for every patient. Table 18–2 highlights classes of glaucoma medications to avoid with certain medical conditions and medications.

Future Considerations

What Are Some Possible Agents Being Developed for the Treatment of Glaucoma?

These include cytoskeletal agents, lipids, neuroprotective agents, and calcium channel blockers.

Cytoskeletal agents include latrunculins, cytochalasins, ethacrynic acid, protein kinase inhibitors such as staurosporin, and calcium chelators.[99,100] In general, these agents seem to work by altering the architecture of the conventional outflow channels in the eye to create better outflow. Actin cytoskeleton disorganization in the trabecular meshwork can increase the outflow facility, which appears to be the mechanism of these agents.[100] In monkey eyes treated with latrunculin-A, outflow facility was significantly increased without serious adverse side effects. Mechanism seems to be destabilization of the actin filament network, decreasing outflow resistance.[101] Another class of agents has been designed to degrade hyaluronic acid, which seems to improve aqueous outflow.[102] Preliminary studies have been encouraging.

Several ocular hypotensive lipids are being actively investigated. One of these agents, AGN-192024 0.03%, used once daily was compared to latanoprost 0.005% once daily and found to offer at least equal efficacy in lowering IOP and

better diurnal pressure control.[103] The lipid was found to be well tolerated and safe, with the most common side effect being mild hyperemia.

Ethacrynic acid is a loop diuretic that has been under investigation in the treatment of glaucoma since the late 1980s.[104] Studies have shown that it may increase outflow facility by creating changes in Schlemm's canal that may be related to its inhibition of microtubule assembly. The initial study showed that it significantly increased outflow facility acutely in human cadaver eyes with no obvious toxic effects.[104] A topical ethacrynic acid ointment was found to effectively lower IOP in monkeys by the fifth day, and its efficacy was similar to that of timolol 0.5%. Mild eyelid edema, conjunctival hyperemia, discharge, and one corneal erosion were noted.[105] Introduction of the drug has been limited by its potential for local and systemic toxicity and short duration of action. The other agents have similar challenges and potential at this time.

What Is the Role of Calcium Channel Blockers in the Treatment of Glaucoma?

Calcium channel blockers act by binding membrane-bound calcium channels and inhibiting the influx of calcium. These drugs have been under investigation for potential ophthalmic uses due to the interest in vasospasm in normal tension glaucoma and their ability to lower IOP. Studies have had variable results on the topical effects of verapamil, most demonstrating a significantly lower IOP.[106,107] Topical administration was found to increase facility of outflow by 64%.[106] However, an earlier study has shown that the topical use of nifedipine, diltiazem, and verapamil caused transient elevations of IOP in both humans and rabbits.[108] The increase in IOP was found to be greater in rabbits than humans and may have been related to the detected increase in blood flow to the treated eye, causing a greater production of aqueous. Another investigator used a similar protocol with a much lower concentration of topical verapamil—0.125% versus 1 to 2%—and found a significant reduction in IOP.[109] A biphasic response to verapamil may be present, and even with the smaller concentrations a contralateral effect was present. It remains clear that a more conclusive study needs to be performed before topical agents will have any role in the treatment of glaucoma.

Systemic administration of nifedipine showed improvement and stability in visual fields of some normal-tension glaucoma patients.[110–112] One study demonstrated that normal-tension glaucoma patients had a much lower rate of progression on their visual fields—11% versus 56%—than controls not taking oral calcium channel blockers.[110] Similarly, the treated low-tension glaucoma patients showed no progression of optic nerve damage compared to 44% who showed progression without the calcium channel blocker. No benefit was found in taking calcium channel blockers for open-angle glaucoma.[110] One of the larger studies investigating calcium channel blockers found no benefit in visual field, IOP, or optic disc changes in 83 treated patients compared to a control group of patients.[113] No detrimental side effects were noted.

A series has shown improvement of visual fields in patients taking systemic calcium channel blockers. Patients with normal-tension glaucoma felt to be associated with vasospasm tended to show improvement in visual field while taking calcium channel blockers.[111] Vasospasm was determined by improved

cold recovery rate in peripheral vessels while on nifedipine. Focal defects were the least responsive. A study comparing repeat performance of visual fields and measured color vision found that some normal-tension glaucoma patients on calcium channel blockers had significant performance-corrected improvement.[112] Another study failed to show uniform improvement in visual field tests, but noted significant improvement in contrast sensitivity in patients who showed improved retrobulbar blood flow with nimodipine administration.[114] A newer calcium channel blocker, nilvadipine, has demonstrated potential for treatment in normal-tension glaucoma.[115] It has the advantage of not lowering blood pressure in normotensive patients while increasing perfusion of the optic nerve, retina, and choroid in patients with normal-tension glaucoma. This study suggests that calcium channel blockers may be beneficial for a certain subgroup of normal-tension glaucoma patients. More conclusive and prospective studies are needed before calcium channel blockers are routinely applied to the treatment of patients.

What Has Generated All the Interest in Neuroprotection?

It is well known that even in spite of good treatment, IOP reduction, and compliance, many patients will go blind from glaucoma.[116] This has created a desperate search for a better way to control the damage from glaucoma. Although the etiology of visual loss in glaucoma is multifactorial and not clear in many instances, ophthalmologists concur that it is caused by the death of retinal ganglion cells. Neuroprotection therapy could potential prevent visual loss in any glaucoma patient independent of which type of glaucoma the patient has.[117]

Areas of research include heat shock proteins,[118] glutamate toxicity, and many others. Hyperthermia prior to ischemic exposure has been found to be neuroprotective in the rat model. Isolation of these protective substrates may yield a source of neuroprotective agents.[118] Brimonidine has come into the limelight recently due to a study with axonal rat crush injury that demonstrated axons survived better when treated with brimonidine.[119] Retinal ganglion cells and nerve fibers treated with brimonidine showed significantly less cell death than those treated with timolol or the saline control. Additionally, the neuroprotective effect was blocked by rauwolscine, the α^2-adrenoreceptor antagonist.[119] Additional studies have also shown that brimonidine was also protective against several other mechanisms of nerve injury including light stress, ischemia, and calibrated nerve compression.[120] This is an actively researched area by the pharmaceutical company, but as of yet no clinically relevant studies have been completed and the information is only theoretical at this point.

N-methyl-D-aspartate (NMDA) receptor antagonists are thought to have therapeutic potential in numerous central nervous system disorders ranging from acute neurodegeneration, such as strokes and trauma, to chronic neurodegeneration, such as Parkinson's disease.[121] Memantine is felt to be one of the most well-tolerated drugs in this class. It has become of interest in treating glaucoma because it was shown to block toxicity caused by glutamate.[122] Clinical studies using memantine to treat glaucoma are presently in progress. Investigators found that the NMDA antagonist eliprodil was protective against glutamate cytotoxicity in retinal neurons.[123]

Similar studies of medications currently used yielded neuroprotective effects based on the above models. A study using a rat retina showed that betaxolol is a neuroprotective agent and attenuates the effects on the retina induced by raising the IOP to simulate an ischemic insult, as may occur in glaucoma.[124] Further study of betaxolol revealed that in addition to its IOP-lowering effects, it has calcium channel blocker activity that may enable it to be neuroprotective.[125]

How Can the Proliferation of Medications and Studies Enable Better Treatment of a Glaucoma Patient?

Editorials, trade journals, review journals, peer-reviewed journals, and professional meetings find that glaucoma treatment is a marketable subject. There are now more treatment options than ever before, but still some patients go blind. An editorial summarized the situation well by saying the power of experience must be carefully integrated with the databased protocols and the constraints of preferred practice plans.[126]

How Do Physicians Initiate, Modify, and Continue Therapy?

Perhaps the most important aspect of treatment is education and support. Clinicians are trained to rely heavily on objective indices such as IOP, perimetry, optic nerve fiber layer, and nerve head analysis and vision. Treatment has a major impact on the patient's life. Recent studies have shown that glaucoma patients have a lower quality of life than healthy peers. Patients with glaucoma experience fatigue, and their social satisfaction and physical and mental health were significantly worse than controls.[127] Knowing how glaucoma is affecting the life of the patient enables the physician to tailor treatment to the needs of the patient. The Glaucoma Symptom Scale has recently been introduced as a brief and reliable estimate of the symptoms associated with glaucoma and its treatments.[128] A recent retrospective study found that the average cost of treating a newly diagnosed glaucoma patient will be about $2,100 during the first 2 years.[129] Whatever the treatment course you follow it will have a major impact on your patients life. Knowing how glaucoma is effecting the lives of our patients will enable a treatment to be tailored that works best for each individual patient.

How Can Patients Become Better Informed?

In-office videos and handout literature are available to inform patients about their treatments and disease. More resources are becoming available on the World Wide Web, which enable patients to become more involved in their own treatment. Good web sites include:

- The Glaucoma Foundation—*www.glaucomafoundation.org/info*
- Glaucoma Research Foundation—*www.glaucoma.org*
- American Academy of Ophthalmology—*www.eyenet.org*
- Prevent Blindness America—*www.preventblindness.org*
- The National Eye Institute Information Center—*www.nei.nih.gov*

The patient's active involvement in treatment increases compliance.

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◆ 19 ◆

Principles and Complications of Surgical Therapy for Glaucoma

William H. Lee, III

This chapter is intended to be used by beginning surgeons as a summary guide in their preparation to work under the direction of an experienced glaucoma surgeon. Although this chapter includes a specific step-by-step summary of variations on many surgical techniques, it is not intended to be used as a "field guide" for novice surgeons to independently perform these procedures. Any such attempt would be unrealistic given the difficulties of glaucoma surgery.

Definition

Why Should Surgical Therapy Be Considered For Glaucoma?

When medical therapy is insufficient in lowering intraocular pressure (IOP) enough to protect a patient's optic nerve over their estimated lifetime, then surgical therapy is indicated.

What Is the Goal of Surgical Therapy?

The goal of surgical therapy is to lower IOP enough to minimize the risk of further optic nerve damage. Surgical therapy is usually reserved for those who remain at high risk for further optic nerve damage despite maximally tolerated medical therapy. As with medical therapy, surgical procedures lower IOP by either increasing outflow or reducing aqueous production (Tables 19–1 and 19–2).

Clinical Pathways in Glaucoma. Edited by Zimmerman and Kooner.
Thieme Medical Publishers, Inc., New York © 2001.

Table 19–1. Procedures That Increase Aqueous Humor Outflow (Most Common Glaucoma Surgical Treatments)

Argon laser trabeculoplasty (ALT)
Laser peripheral iridotomy (LPI)
Laser gonioplasty
Trabeculectomy
Setons

Table 19–2. Procedures That Reduce Aqueous Humor Production

Cyclocryotherapy
Nd:YAG cyclophotocoagulation (YCP)
Diode cyclophotocoagulation
Endocyclophotocoagulation

Note: These procedures destroy ciliary body tissue and are less commonly used.
Nd:YAG = neodymium:yttrium-aluminum-garnet.

When Is An Outflow Procedure Planned Versus a Procedure that Reduces Aqueous Production?

Generally speaking, procedures to increase outflow (Table 19–1) are the first-line surgical treatment for glaucoma. These procedures are considered safer, more successful in preservation of vision, and less painful. Procedures to reduce aqueous humor production (Table 19–2) are reserved for cases that are refractory to interventions that increase outflow because reducing aqueous humor production means destroying ciliary body tissue, which is often difficult to titrate and thereby carries a higher complication rate of phthisis bulbi and blindness. Transient pressure spikes and pain are also not uncommon complications. Furthermore, with the exception of endolaser treatment, the cyclodestructive procedures cause varying degrees of damage to the trabecular meshwork and other outflow channels, which is another factor in the unpredictability of these procedures. Practically speaking, the cyclodestructive procedures (Table 19–2) are reserved for near end-stage eyes. These patients usually have extensive subconjunctival scarring and are poor candidates for other surgeries. With the advent of the Baerveldt and other more improved shunt devices, there are fewer indications for resorting to cyclodestructive procedures.

Epidemiology and Importance

Why Are Surgical Therapies Considered Earlier in Glaucoma Nowadays?

Over the last 10 years, there has been a trend toward earlier treatment with laser and surgery.[1,2] We are beginning to understand that to fully protect the optic nerve over a patient's lifetime, lower IOPs than previously thought may

be required.[3] In addition, our surgical techniques have improved. With guarded trabeculectomies and planned postoperative suture lysis, there are fewer serious complications. With antimetabolites such as 5-fluorouracil (5-FU) and mitomycin C (MMC), there are higher bleb success rates as well as lower average postoperative pressures. These developments have led some to advocate earlier surgical intervention.[4–8]

At the same time, however, medical therapy has likewise improved. Combination drug therapy is now often capable of producing fairly low IOPs, fewer side effects, and higher compliance rates. In this country, primary surgical treatment as opposed to medical therapy is still controversial, even among the experts.[9]

Does the Incidence and Success Rate of Glaucoma Surgery Vary in Different Countries and Races?

In Europe there has been an even greater trend toward earlier surgery.[5–8] This may be because of the more homogeneous population of fair-skinned people, who tend to have fewer surgical failures than the darker races. Consequently, surgical success rates seem to be higher abroad, and higher success rates favor correspondingly earlier surgical intervention.

Another factor is that many of the countries in Europe have a more socialized form of medicine with even greater financial restraints. Early surgery seems to be more cost-effective in the long run than lifelong multimedical therapy.[10]

Interestingly enough, a similar situation occurs in Africa, where the high cost and poor availability of medications makes primary surgical intervention a more likely treatment.[11] Also, although blacks have a higher rate of scarring and thus a higher rate of bleb failure, their increased risk of blindness and earlier onset of disease would suggest that a higher prevalence of surgical intervention would be needed.[12] One study found the recently popular procedure of viscocanalostomy highly successful in this group.[13]

In the United States, however, one study suggests that blacks have a correspondingly lower prevalence of surgical intervention than one would predict on the basis of the prevalence of glaucoma.[14] According to this study, the prevalence of glaucoma in the United States is four to six times higher in blacks than in whites and yet the rates of surgery are only 2.2 times higher for blacks than whites. This means that there is a 45% lower than expected rate of glaucoma surgery for blacks than would be predicted by the rates for whites. This finding may not be as surprising considering the lower success rates of trabeculectomy for blacks.

A similar situation was found in a study of the elderly population in the United States. Surgical treatment rates for this group were proportionately less than expected when compared to the prevalence of severity of glaucoma in this age group.[15]

Other racial differences have also been observed. A recent study found blacks did better with initial argon laser trabeculoplasty (ALT) before resorting to trabeculectomies.[16] Whites, on the other hand, fared better in the long-term by proceeding initially with trabeculectomies and using ALT (and subsequent

repeat trabeculectomy) as the backup protocol. ALT has also been used quite successfully as initial primary therapy in Egypt, where socioeconomic factors make other treatments more impractical.[17] No doubt, socioeconomic factors and the availability of eye care greatly influence treatment patterns both in the United States and elsewhere.

Diagnosis and Differential Diagnosis

When Does Surgical Intervention Become Essential in Glaucoma?

If medical therapy fails to prove adequate for protection of the optic nerve and visual fields, it is important to reevaluate the patient's target IOP and overall condition. Is the patient compliant? Has the maximally tolerated medical therapy been completely explored? Could high blood pressure, atherosclerosis, nocturnal hypotension (from excessive nighttime systemic beta-blocker agents), anemia, a long-forgotten past hypovolemic/hypoxic episode, or even an undiagnosed intracranial tumor have been contributing factors?

How Is the Decision Made to Intervene Surgically in Glaucoma?

If high IOP is thought to be a major problem, it is always a good idea to repeat gonioscopy prior to considering laser or surgical intervention. It is not uncommon for what was once thought to be primary open-angle glaucoma (POAG) to slowly progress to an accompanying component of chronic narrow-angle glaucoma (especially in blacks) or phacomorphic glaucoma (especially in elderly hyperopes with nuclear sclerotic lens changes). Occasionally, neovascular glaucoma (NVG) is initially overlooked in its earlier stages in patients with diabetes, carotid artery occlusion, or retinal vein occlusion.

Treatment and Management

How Does One Decide Which Procedure to Do First?

Figure 19–1 outlines the management of patients when maximal medical therapy fails to adequately control IOP. If gonioscopy reveals an open angle, ALT is the first procedure of choice. If this fails, surgical guarded trabeculectomy is indicated. Antimetabolites are used in conjunction with primary trabeculectomy in many patients who are at high risk for failure (younger patients, blacks, patients with a history of prior eye surgery, etc.). Antimetabolites are strongly indicated in patients who have had a prior failed trabeculectomy. If two or more guarded trabeculectomies have failed, or if a patient has neovascular glaucoma, a seton device is usually indicated. Antimetabolites probably should not be used with seton devices.[18]

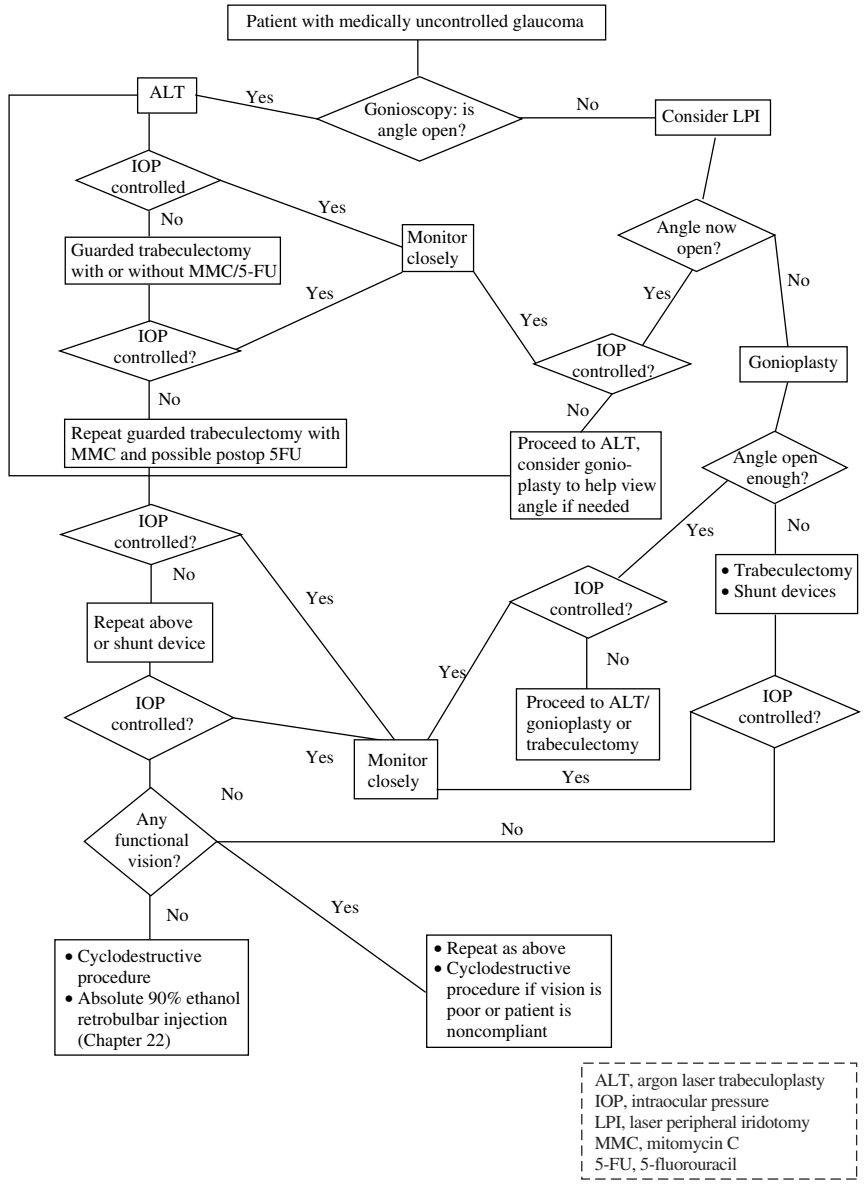

Figure 19–1. Management of patients with medically uncontrolled glaucoma.

If gonioscopy reveals the angle to be closed, then compression gonioscopy can be helpful. If the angle compresses open, a laser peripheral iridotomy (LPI) will likely be helpful. If after iridotomy the angle opens but the IOP remains elevated, consider ALT or guarded trabeculectomy (probably with an antimetabolite). If the angle is not open following LPI, then the patient may have plateau iris (rare) or phacomorphic narrowing (more common). Phacomorphic narrowing will have a convex or volcano iris plane in contrast to the flatter iris plane of plateau iris. Gonioplasty is often helpful in patients with phacomorphic narrowing and may be useful in facilitating visualization prior to ALT in

these patients. If this fails to open the angle, and especially if cataracts are present, lensectomy with or without trabeculectomy is then indicated for phacomorphic glaucoma. If peripheral iridotomy and gonioplasty fail to open the angle, and a phacomorphic component is not present (the lens is clear and relative eye size is proportionate), then the patient likely has plateau iris or other angle deformity and may require trabeculectomy.

Surgical intervention is indicated, and seton procedures are likely favored over trabeculectomy when the angle is "zippered shut." Old NVG or extensive peripheral anterior synechiae (PAS) from trauma or iritis are other examples of chronic closed-angle cases that do not respond to LPI or gonioplasty. Seton devices in these patients may be a better choice than trabeculectomy if the surgeon has experience with these devices. If a trabeculectomy is performed instead, then an antimetabolite should be used in most of these cases, unless contraindicated.

What Are the More Common Types of Laser Therapy for Glaucoma?

The common types of laser therapy for glaucoma are enumerated in Table 19–1.

What Are the Indications for ALT?

ALT is the most common surgical treatment for POAG and has also been advocated as an initial therapy for POAG.[17,19] Indications for proceeding with ALT vary according to the subtype of glaucoma. Older patients seem to respond more favorably and with fewer side effects than younger patients. Traumatic glaucoma cases respond less favorably. Generally speaking, laser intervention is indicated when medical therapy is inadequate or poorly tolerated due to side effects or noncompliance. When properly applied in appropriate candidates, ALT is generally considered as safe and effective as any single glaucoma medication. Although many laser types have been used, the argon laser is by far the most common laser. Diode lasers are effective and becoming more common.[20]

What Is the Mode of Action of ALT?

Theoretically, ALT stimulates division, as well as metabolism, of the trabecular meshwork (TM) endothelial cells responsible for active transport of aqueous.[21] Historically, a second theory mentions the possibility of a mechanical opening of the TM fibrils.[22] This may occur between the areas where the laser is applied (i.e., shrinkage of some tissue may stretch open collateral tissue). Also, shortening of the trabecular band over 360 degrees may open up the collapsed meshwork and/or Schlemm's canal.

What Are the Principles of ALT?

Generally, we treat half of the functioning angle per session. Usually, ALT is limited to one or two applications per eye over a patient's lifetime. If the first treatment has little effect, and assuming it was properly applied, then it is less

likely that a second treatment will help. If the first treatment involving 180 degrees of the angle was successful, but over time the IOP has again risen, then it is reasonable to attempt another treatment in the remaining 180 degrees of TM. Do not treat if you do not have a clear shot at the TM; hitting the peripheral iris in the angle will lead to extensive formation of PAS. Avoid treating an area of scarred angle or an area of PAS. Try to treat only the functioning angle as identified by an area with some pigmentation in the TM. Atrophic parts of the TM are distinctively nonpigmented. They take up laser poorly and, even if treated, provide minimal if any effect. It is not worth treating these areas.

Is There a Need for Medical Prophylaxis Before ALT?

If not otherwise contraindicated, pre- and postlaser treatment with Iopidine 1% (apraclonidine 1%) can significantly reduce chances of pressure spikes following both ALT and LPI.[23] Alternatively, some surgeons are using Alphagan (brimonidine tartrate 0.2%) as a substitute, although one must be aware that the pressure-lowering effect may not be as great. Cooling the eye (ice packs) is also effective, but most find this less practical.

What Is the Procedure for ALT?

The procedure for ALT is as follows:

- Preoperative apraclonidine 1% is given at least one half-hour before the procedure.
- Focus both oculars so aiming beam is parfocal.
- Topical anesthesia is delivered and the Goldmann lens is used to view the angle.
- The dye laser is "tuned" to the all-green mode or the argon laser is set on the green mode.
- Spot size is 50 μm.
- Time is 0.1 seconds.
- Power settings vary with different lasers and degrees of angle pigmentation. A common initial power setting in a medium pigmented eye with a dye laser in the green mode is between 200 and 400 milliwatts (mW). The power is adjusted to just produce a white blanch at the juncture of the anterior TM (nonpigmented) and posterior TM (pigmented). If a bubble is produced for a microsecond, then the laser power is turned down. Conversely, if no blanch is seen, then the power is turned up. This assumes the surgeon is in a functioning (not atrophic) angle. It also assumes that the argon aiming beam is well focused and centrally located within the gonioscopic mirror of the Goldmann lens, and that the target is the juncture of the nonpigmented and pigmented trabecular meshwork. If the desired effect is not seen, the laser is turned up or down by 50-mW increments until the desired target intensity is reached.
- Darker pigmented TM will absorb more laser and therefore requires less energy.
- Lighter pigmented TM will absorb less laser and therefore requires more energy.
- The atrophic angle will not have pigment and will not take up laser.

- Aim for the junction of the anterior TM (nonpigmented) and the posterior trabecular meshwork (pigmented). This normal anatomy is seen in areas of functioning angle. If it is not well demarcated, then it is likely not worth treating that area!
- The number of shots varies according to how much functioning angle is viewable. Most surgeons leave a space equal to the width of the aiming beam between each laser application. Assuming the total angle is viewable and normal in appearance, the average number of applications per 180 degrees of treated angle is approximately 45 shots.
- Apraclonidine 1% is given immediately postop; prednisolone acetate 1% (Pred Forte) or loteprednol elabonate (Lotemax) are given q.i.d. for 4 days, or as needed.
- IOP is checked at 1 hour and at 1 to 7 days postoperatively.

How Effective is ALT?

Eighty percent of eyes initially respond with a significant reduction in IOP. After 5 years, 50% of eyes are thought to still have a measurable pressure lowering effect.[24]

What Are the Complications of ALT?

The most common side effect of ALT is a transient increase in IOP (pressure spike) and/or inflammation (cells and flare). Preoperative and postoperative apraclonidine 1% and postop antiinflammatory agents have greatly reduced the chance of these side effects.

What Are the Indications for LPI?

LPI is the primary treatment of choice for acute narrow-angle glaucoma and chronic narrow-angle glaucoma due to pupillary block. It has a more subjective use in the prophylaxis for prevention of narrow-angle glaucoma in patients at high risk. Likewise, there is some indication for prophylaxis in patients with relative pupillary block (intermittent narrowing of the angles). More recently, LPI has been found useful in select patients with pigment dispersion syndrome.[25] It does not resolve plateau iris configuration, but this diagnosis is usually not made until LPI has already been attempted because it is a diagnosis of exclusion.

What Is the Mechanism of Action of LPI?

LPI relieves the buildup of pressure in the posterior segment due to relative or absolute pupillary block. By providing an alternate route for aqueous humor to pass from the posterior segment to the anterior segment, there is no longer pressure buildup behind the iris from an occluded pupil. In the pigment dispersion syndrome, a transient increase in the pressure of the anterior chamber compared to the posterior chamber can push the midperipheral iris back onto the zonules and cause dispersion of pigment in some patients. An iridotomy theoretically equalizes the pressure gradient in these cases.

How Is LPI Performed?

LPI can be accomplished with the yttrium-aluminum-garnet (YAG) or argon laser. The YAG laser penetrates the iris quicker and is the most common type used. The argon laser is still sometimes used to pretreat (before the YAG laser), to cut down on the incidence of iris bleeding. This may be especially helpful in patients on coumadin or aspirin therapy. Argon lasers are quite poor for penetrating lightly pigmented irides and YAG lasers will often be necessary in these eyes.

What Are Some Principles to Consider in Site Selection of LPI?

- Avoid any surface iris vessels.
- Look for deep crypts to reduce the amount of tissue through which the laser has to penetrate.
- Apply the laser at 11 o'clock or 1 o'clock on the peripheral iris. The purpose of having the iridotomy superiorly is so that the upper lid will cover the iridotomy and prevent monocular diplopia or glare. The purpose of treating at 11 o'clock or 1 o'clock as opposed to 12 o'clock is that lasers sometimes form bubbles. Bubbles can obscure the view of the area being treated. Bubbles will usually float up to the 12 o'clock peripheral iris.
- Site selection is of major importance. The goal is to be peripheral enough to avoid hitting the lens. (In fact, an LPI that has underlying lens apposition is useless.) At the same time, if you are too peripheral, the view will be clouded by the peripheral haze of the cornea. The cornea runs more obliquely and is thicker (and therefore more opaque) at the far periphery, and so visualization at the far periphery is poor. Also, because of the shallowness of the chamber in this location, corneal endothelial damage is more common at the far periphery.

What Are Some of the Specifics in Performing LPI?

- Apply apraclonidine 1.0% preoperatively.
- Apply pilocarpine 1.0% preoperatively to flatten iris.
- Apply Abraham eccentric lens.
- Set YAG power to 4–5 millijoules (mJ) on double burst mode and apply laser.
- Refocus deeper and reapply laser until penetration achieved.
- Give apraclonidine 1.0% again postoperatively.
- Check IOP at one hour and then as needed.
- Start topical steroids postoperatively for 4–7 days.

What Are Some Other Considerations When Performing LPI?

If the laser penetrates full thickness, then a pigmented fluid wave will be visualized coming forward through the iridotomy site. If this is not seen, refocus at a new depth of the same site and reapply laser. Remember that as one goes posterior into the iris and approaches the posterior segment, the power setting should be reduced to avoid posterior segment damage.

With a power setting of 4 to 5 mJ depending on iris thickness, and in the double burst mode, a patent YAG LPI is usually accomplished in one to three applications. Occasionally, more applications are needed. It is best to wait for the pigment to clear after one shot before shooting again. If moderate pigment is dispersed after three or four shots in an elective procedure, it is sometimes best to postpone further laser treatment for another time to prevent pressure spikes. If it is clearly evident that progress is not being made, it is usually best to try a different site. Complementary argon laser treatment in dark, thick irides is sometimes helpful. Likewise, supplemental argon laser treatment is very helpful to stop unexpected iris hemorrhaging that sometimes occurs during a YAG laser procedure. For these reasons it is ideal to have both lasers located in the same room for these reasons. Very rarely, one may have to resort to surgical iridectomy in patients with thick irides.

What Are the Complications Associated with LPI?

Hemorrhaging and pressure spikes are the most common complications. If a hemorrhage occurs during laser treatment, then gentle pressure to the globe with the Abraham lens will often stop the bleeding. Continue holding pressure for a minute and then recheck to see if it is still bleeding. This can be repeated several times. If this fails to stop the bleeding, it is best to proceed with argon laser cautery to the area.

Pressure spikes are usually controlled medically (may require mannitol). Patients should be warned, however, that rarely a dangerous pressure spike may occur and necessitate trabeculectomy.

How Effective Is LPI?

Almost always, a single, patent iridotomy is successful in preventing or relieving pupillary block. The degree of success for treating select patients with pigment dispersion syndrome is not yet known.

What Are the Indications for Argon Laser Gonioplasty?

A gonioplasty may be indicated when angle crowding of the iris persists in a patient with narrow-angle glaucoma who has already had a peripheral iridotomy. Usually, this occurs in patients who have a superimposed degree of phacomorphic or plateau iris crowding. Also, it is often used to facilitate visualization of the angle prior to ALT in these patients. Argon laser gonioplasty is used usually as a temporary measure in patients who are not yet otherwise ready for cataract surgery or combined cataract/glaucoma surgery.

What Is the Mechanism of Action of Gonioplasty?

The procedure uses the argon laser to burn areas of iris stromal tissue in the peripheral iris. This results in contracture of tissues and pulls the peripheral iris from the angle. In cases with some degree of phacomorphic component, it may flatten and stiffen the midperipheral iris to reduce its anterior bulge.

Likewise, in plateau iris configuration and nanophthalmos, it may prevent appositional angle closure.

What Are the Principles of Gonioplasty Treatment?

- Avoid iris vessels because sectoral iris atrophy may result.
- Try to treat only a quadrant or perhaps one-half of the iris at a time in order to avoid pressure spikes.
- Keep laser burns in a radial row of two to three burns. Visualize what part of the iris is moving with each application. You should be able to see iris pulling away from the angle as it is flattened. If you see iris stretching the pupil open, then you need to be more peripheral.

How Is Laser Gonioplasty Performed?

- Pretreat with apraclonidine 1%.
- Apply the Abraham lens.
- Set argon laser to green wavelength.
- Spot size is 100 to 200 μm.
- Power setting is 100 to 200 mW. (Use the least amount of power to produce movement of collateral iris tissue. It will also produce a small white blanch.)
- Treat in radial rows of two to three burns. This usually means 10 to 12 shots per quadrant.
- Apply apraclonidine 1% postoperatively.
- Recheck eye pressure 1 hour following procedure.
- Administer a drop of cyclogyl 1% to prevent posterior synechiae.
- Administer prednisolone acetate 1% every 4 hours for 4 days or as needed.
- Recheck 1 to 7 days postoperatively.

What Are the Complications Associated with Laser Gonioplasty?

The most common complication is pressure spike, which can usually be handled medically. All patients should be warned of the chance for iris atrophy in the sector that is being treated. This is especially true if a radial iris vessel is treated. Patients should know that this may change the color of their iris.

When Is Surgical Trabeculectomy Indicated?

Surgical trabeculectomy is indicated when optic nerve function remains threatened by current IOP and medical and laser treatments have been inadequate or poorly tolerated.

Why Not Proceed Straight to Surgery?

Using surgery as the initial treatment for glaucoma has been popular abroad.[1] It is postulated that surgery is more successful in some of these communities because of the homogeneous population. Moreover, socialist medical environ-

ments may be more cost conscious. In some cases, multiple medical therapy may simply be too expensive as a lifetime treatment. It is also known that medication and preservatives in topical eye drops taken long-term can increase bleb scarring and thereby reduce surgical success.[26,27] Even ALT has been linked as a possible cause of encapsulated blebs following filter surgery.[28] Another study found male gender to be a risk factor for bleb encapsulation, but the risk from ALT was not statistically significant in that study.[29] All of these factors have generated a push by some toward primary trabeculectomy.[1]

In this country, patients are living longer and our attitudes are changing as to how low pressure must remain in order to reasonably sustain optic nerve function for a given patient's lifetime. We are being more aggressive with IOP and are proceeding with surgery at earlier stages than in the past. It is important to remember, however, that the incidence and severity of complications with glaucoma surgery is still relatively high compared to other ophthalmic procedures (e.g., cataract surgery, refractive surgery, etc.). Also, success is much less predictable in glaucoma surgery compared to other eye procedures because outcome is so dependent on each patient's individual scarring response (determines bleb success) and preexisting degree of outflow obstruction (determines how much filtration a given surgery must achieve in order to lower IOP). Furthermore, many of our latest and most potent topical medications (Xalatan, Alphagan, Cosopt, to name a few) were not available when the trend toward primary trabeculectomy began with the "Moorfield studies" of the 1980s.[5–8]

Even with the most successful glaucoma surgery, it is common to have some increase in the cloudiness of the lens.[30] In addition, many patients will be forever symptomatic because of their well-functioning bleb (foreign body sensation). Furthermore, all patients with a functioning bleb are at a lifetime risk for bleb infection and possible endophthalmitis. For all of these reasons, surgical trabeculectomy is generally reserved for patients who remain at high risk despite prior medical and laser therapy.

What Is Guarded Trabeculectomy?

There are an infinite number of variations of glaucoma filtration surgery (Table 19–3). The guarded trabeculectomy is the procedure of choice for most patients. These procedures can utilize either a fornix-based conjunctival incision (conjunctiva is opened at the limbus) or a limbal based conjunctival incision (conjunctiva is opened about 10 mm posterior to the limbus and dissected forward). Each type of conjunctival incision has advantages and disadvantages with corresponding proponents and opponents.

The majority of trabeculectomies are performed under local anesthesia using peribulbar or retrobulbar anesthesia. A peribulbar block is considered safer than a retrobulbar block and therefore is usually recommended. Usually a 1:1 mixture of lidocaine 2% with Marcaine 0.75% is used along with Wydase. More recently, topical anesthesia combined with localized subconjunctival lidocaine 2% and intracameral nonpreserved lidocaine 1% has been occasionally used. This method does not work in all cases because of the lack of adequate akinesia. General anesthesia is sometimes advocated in monocular patients at high risk for retrobulbar or peribulbar anesthesia.

Table 19–3. Glaucoma Filtration Surgeries

Guarded trabeculectomy

First described by Sugar in 1961 and later made popular by Cairnes[32] in 1968, this procedure is the most common type of filter surgery performed today. The technique uses a block of sclera to partially occlude or "guard" the egress of fluid from the anterior chamber into the subconjunctival space. This modification greatly reduces the chance of complication due to hypotony in the early postop period. It also reduces the risk of endophthalmitis in the late postop period that was sometimes seen with the thin cystic blebs of full thickness trabeculectomies.

Unguarded or full-thickness trabeculectomy

This was made popular by MacKenzie in 1830, and early 20th century variations by LaGrange and Holth were used widely until the 1970s.[33] It is rarely used today due to the high incidence of the above-mentioned complications.

Non-penetrating filtration surgery

First described by Zimmerman et al.[34,35] in 1984, this is a group of relatively new procedures that leave the innermost fibers of the trabecular meshwork intact. These procedures use a superficial scleral flap just as in traditional guarded trabeculectomy. Under this flap a very deep sclera block is dissected and excised, thereby directly exposing scleral spur. As this dissection is carried to the limbus, Schlemm's canal and the inner wall of uveal trabecular meshwork (TM) is exposed. Aqueous from the anterior chamber can be seen "percolating through" the thin membrane of uveal TM or peripheral Descemet's membrane. The superficial sclera block is then sutured back in place. Often collagen implant or viscoelastic is left underneath the superficial scleral flap to maintain an intrascleral reservoir.

Being extraocular procedures, the nonpenetrating surgeries may have fewer complication rates of cataract formation, postop hypotony, and uveitis. Because no peripheral iridotomy is performed, bleeding is less of a problem. These relatively new procedures may become increasingly important in the future but they are technically challenging, and long-term success rates are not yet known.

A more recent version of this procedure by Stegmann et al.[13] called viscocanalostomy is performed in a similar manner, but adds the injection of viscoelastic directly into Schlemm's canal during the procedure.

Shunting or seton devices

These were first described by Molteno[36] in 1969, and have undergone many variations since. There are a number of valved (Krupin, Ahmed) and nonvalved (Baerveldt, Molteno, Schocket) shunts available. Usually, these devices are reserved for patients with failed prior trabeculectomy or a propensity toward scarring such as neovascular glaucoma. They are also indicated for those patients with extreme scarring of the angle. Most of these devices consist of a tube that remains in the anterior chamber and "shunts" aqueous to an external subconjunctival reservoir. The larger the surface area of the reservoir, the lower the postoperative IOP. These devices require a higher degree of surgical expertise and are fraught with their own individual set of complications. They are invaluable, however, in patients who are at high risk for trabeculectomy failure.

How Is a Guarded Trabeculectomy Performed?

Guarded trabeculectomies can be done in many ways. The scleral tunnel technique described below is the safest and most reproducible procedure. Because it uses the traditional "cataract" scleral tunnel technique, it is highly adaptive

to combined cataract/glaucoma surgery. The scleral tunnel technique allows for the most uniform and reproducible scleral flap.

A cornerstone to the concept of this surgery is that the scleral flap will be made almost watertight with the intention of performing laser suture lysis postoperatively. This greatly reduces the biggest risk for complications in glaucoma surgery, namely postoperative hypotony. This concept has revolutionized glaucoma surgery in that good filtration can be obtained without many of the risks encountered with earlier techniques, such as full-thickness trabeculectomy, Elliot's trephine, cyclodialysis, etc.

Be sure to prepare the patients beforehand that they will likely have laser suture lysis between 1 and 4 days following surgery. They should be informed that this is a routine part of this type of glaucoma surgery and that although it is an extra step, they are receiving the safest form of surgery.

What Is the Mode of Action of Trabeculectomy?

The goal of glaucoma filtration surgery is to produce a fistula from the anterior chamber through the sclera to allow a controlled amount of aqueous to egress into the subconjunctival space (thus lowering IOP). The aqueous is then reabsorbed into the bloodstream by subconjunctival venules. Transconjunctival evaporation also likely occurs.

What Are the Principles of the Trabeculectomy Procedure?

- Administer inferior and superior peribulbar block; apply intermittent digital pressure until the globe is soft.
- For sterilization, prep with a 50% Betadine solution. Also use it topically to irrigate the cul-de-sac. (Use 25% topically if the case is being done under topical anesthesia.)
- Use talc-free gloves to reduce the chance of Tenon's cyst formation.[37]
- Insert a wire lid speculum.
- Pass an 8-0 Vicryl suture through the superior peripheral cornea about 3 mm from the limbus as a corneal traction suture. (Inferior corneal traction sutures also work well if tucked below the lid speculum.)
- For a fornix-based flap, perform a conjunctival peritomy. This is made about 8 to 10 mm in chord length.
- Take special care not to tear the conjunctiva. Use only conjunctival forceps (which has ridges but not teeth) so that conjunctival edges are not torn.
- At the beginning of the peritomy, a relaxing incision is made by initially entering the conjunctiva 4 mm posterior to the limbus to gain access into the sub-Tenon's space and thereby allow for a sub-Tenon's dissection, because Tenon's ends before the conjunctiva at the limbus. This initial entry should be well away (8 mm) from the intended trabeculectomy site.
- After the initial entry, it is important to dissect sub-Tenon's for the full extent of the conjunctival incision and as close to the limbus as possible. This will expose bare sclera.
- Do not perform aggressive undermining of the peritomy into the quadrants. Just open the conjunctiva enough to allow adequate exposure for

surgery. Further posterior dissection is counterproductive, as it only aggravates the inflammatory response.

- Eraser-tip wet-field cautery is used for bleeders and to lightly blanch the area of the sclera to be incised (sclera flap).
- Use a Beaver blade no. 6600 because this single blade can be used for both steps of the formation of the scleral flap.
- Begin the scleral incision 4 mm posterior to the limbus and parallel to it.
- Use the blade to make a three-quarter depth scleral incision. Stop when the deeper blue hue of the inner sclera is seen. Get a feel for the thickness of the sclera and try to achieve the correct depth within the second or third pass. Make the incision about 4 to 5 mm long.
- Turn the blade over so it is parallel to sclera and insert the rounded tip into the deepest part of the incision. Use a wiggling motion to advance the rounded tip within a single plane (parallel to the sclera surface) and into clear cornea. If too much resistance is encountered as the blade advances, then the established plane may be too shallow. This part of the incision is identical to the typical scleral tunnel cataract incision, which is why it is so well adapted to combined surgery, even though the initial incision is not quite as anterior as with typical cataract surgery.
- Advance the blade until it can be visualized about 2 mm beyond the limbus into clear cornea.
- Widen the scleral tunnel so that it is exactly uniform to the edge of its original scleral entrance incision, that is, 4 to 5 mm wide. If the tunnel is made wider than the incision, it will be difficult to get the sclera flap watertight.
- Use Vannas scissors to open both sides of the tunnel to the surgical limbus. Be sure the scissors blades are exactly perpendicular to the sclera that is being cut. Enter the tunnel flat with one blade of the scissors, and then turn the scissors so the blades are perpendicular to the surface of the sclera (one blade within the tunnel, one blade on top of the sclera) and slide the scissors sideways all of the way to the edge of the tunnel to get this incision as perpendicular and uniform as possible. Usually, it takes three or four snips to get to clear cornea on each side. Go up to but not beyond clear cornea or else leakage may occur here.
- Lift the flap and there should be a uniform direct view of the corneal-scleral junction. At least 1 mm of clear cornea should be viewed anterior to this lamellar junction. If this is not seen, then use the Beaver blade again to establish that length.
- If using MMC, first close the scleral flap and apply 0.2 mg/mL for 2 minutes[38] on top of the scleral flap. 5-FU in a concentration of 25 to 50 mg/mL for 5 minutes also works well and may be safer.[39] Unlike MMC, 5-FU is not a strong alkylator and though toxic to cells of replication (fibroblasts), it has little effect on static cells (sclera). Comparatively speaking, 5-FU is less destructive to scleral and conjunctival tissue and therefore carries less of a chance for late-onset bleb leaks and associated infections. The instrument wipe sponge or corneal light shield[40] provides a more uniform uptake of MMC or 5-FU than does the Weck cell. Cut a 4- × 4-mm piece of this sponge and place it directly over the scleral flap after it has been soaked in the antimetabolite. Care must be taken to make sure that no edges of the conjunctiva touch the sponge. The sponge does not go under-

neath the scleral flap, but simply sits on top of it.[41] After 2 minutes, use a Weck cell to dry the area completely, and then use copious amounts of balance salt solution (BSS) to dilute any remaining antimetabolite. It is helpful to lift the conjunctival edges up so that they are not in contact with the solution while irrigating.

- Use a microsharp blade to create a paracentesis site at the temporal limbus. If topical subconjuctival anesthesia is being used, then inject the nonpreserved intracameral lidocaine 1%.
- If the chamber is at all shallow, then apply a small amount of viscoelastic just at the 12 o'clock site to deepen the chamber just beneath the trabeculectomy. It is not necessary or desired to fill the whole chamber with viscoelastic in most cases.
- To establish the trabeculectomy site, use a microsharp knife (or 2.6-mm keratome if performing phacoemulsification) to enter the anterior chamber beneath the scleral flap. This is done in the same manner as in a paracentesis. The entrance of this incision should be at least 1 mm anterior to the corneal scleral juncture, that is, 1 mm into the cornea and 3 or 4 mm in length. Be sure it is near the center of the overlying scleral flap, and not near its edges.
- If the chamber shallows as this incision is made, then use viscoelastic to focally push the iris back down.
- Insert the Kelly or Holth scleral punch. It must be inserted with the blade open. Be sure it is completely within the eye. (It usually is a tight fit and one feels it "pop through" into the anterior chamber.) Then rotate the instrument so it is directly perpendicular to the scleral plane (rotate the handle upward).
- Once the instrument is perpendicular to the scleral surface, snip out the corneal-scleral junction and proceed snipping bits of tissue into the trabecular meshwork. With each snip inspect the tissue removed, and remove it from the guillotine. If the tissue is carefully inspected, the small pigmented lines of the trabecular meshwork can usually be seen once it is reached. Once the TM is removed, no further punching is needed. Usually, this requires two to three snips posteriorly. Keep the width of the punch excision to a single width. The inner block of corneal-sclera that is removed only needs to be one punch wide to work properly. Two to three punches posteriorly usually penetrate trabecular meshwork, and often into scleral spur.
- As you approach TM with the punch, be sure that the punch does not entrap a peripheral iris roll, iris root, or the anterior portion of the ciliary body. Cutting these will result in profuse bleeding.
- When done properly, heavy bleeding with the above procedure is rare. If it occurs, then Myra cautery or a retinal cautery (pointed tip) will likely be needed for control.
- Use a 0.12 forceps and Vannas scissors to create a small underlying iridotomy. When using the forceps to grasp the iris, it is important to grasp the iris more central than the tissue that presents at the trabeculectomy site to avoid pulling the iris root or cutting the anterior portion of ciliary body or iris arcade. That is, grab a point slightly peripheral to the mid-iris, where the peripheral one-third of the iris meets the central two-thirds.

- Once the iridotomy is made, reapproximate the scleral flap and use BSS on a 27-gauge cannula through the paracentesis site to flush the anterior chamber free of viscoelastic and to establish filtration.
- It is important to prevent the eye from becoming hypotonous (flat chamber) at any point in the case, as this will precipitate anterior displacement of the ciliary body. Use BSS or viscoelastic as needed.
- Next, secure each corner of the scleral flap back down using a 10-0 nylon suture. Cut the sutures on the knot, and try to bury the knot outside of the scleral flap.
- Check filtration by injecting BSS (on a 27-gauge cannula) through the paracentesis and watching the flow rate around the scleral flap. In white patients with nonscarred eyes, there should be almost no leakage at normal pressures. Instead, a white glistening reflex is seen in the scleral groove. If leakage occurs, continue using interrupted 10-0 to make the flap almost watertight. By injecting BSS, an IOP in the mid-teens should be established. In blacks or patients suspected of scarring, slightly more filtration can be allowed. Still the filtration should be a bare trickle, and an IOP of about 10 mm Hg should be maintained after injecting BSS.
- In addition to the corner sutures, often several additional sutures are required to get the scleral flap sufficiently leak-free at normal IOPs. Using BSS through the paracentesis, our goal is usually to establish filtration that allows for an IOP of about 10 to 15 mm Hg. Once this is established, it is a good idea to recheck after 1 or 2 minutes to be assured that the eye is holding that pressure. If so, the end point is reached, and the eye is ready for closure.
- Once the conjunctiva is reapproximated to its original position over the trabeculectomy site (but prior to suturing), it is mandatory to assess the amount of Tenon's capsule over the trabeculectomy site. Remember that the sutures that close the scleral flap must be easily visible through the conjunctiva to allow for suture lysis postoperatively. It is therefore usually necessary to tease away and remove one or two layers of Tenon's capsule beneath the conjunctiva to allow for this. Using a conjunctival forceps to pick up the anterior lip of the incision of conjunctiva, the underlying Tenon's layers can be split away using the Vannas scissors in a blunt dissection method. This must be started at the area of the initial conjunctival relaxing incision where Tenon's capsule and conjunctiva can be separated. By inserting the scissors with tips closed into this potential space, and then spreading with scissors, a plane can be established. Then the scissors can be used to remove this excess tissue above the scleral flap site. Extreme caution must be exercised to prevent buttonholing of the conjunctiva. Irrigation of BSS on a 27-gauge blunt cannula can be helpful to establish this potential tissue plane. Once Tenon's capsule is removed and the translucent conjunctiva reapproximated, the 10-0 nylon should be easily visible through it. (Separate dissection of conjuctiva and Tenon's capsule at the beginning of the case is also an alternative and sometimes is easier.)
- To close the conjunctiva reapproximate it to its original position and hold it in place with a 10-0 nylon (BV needle) at each corner of the original limbal incision. Be sure to include a bit of episcleral tissue so that the conjunctiva

does not retract, and it will be held fast to that spot. Additional interrupted or running 10-0 nylon (BV needle) is then used on any relaxation incisions that were created. With all interrupted sutures, it is best to cut on the knot.

- Now use the Beaver blade to rough up the epithelium of the clear cornea at the limbus overlying the trabeculectomy site so that the conjunctiva will better stick down at the site.
- To keep the conjunctiva from retracting at the limbal site of the trabeculectomy, an anterior circumferential suture is quite helpful, and is used in almost all cases. A 10-0 nylon suture on a spatula needle is passed into clear cornea just central to the limbus at the point where the conjunctiva should adhere. The needle track runs parallel to the limbus. The entrance of the needle is at one side of the trabeculectomy site in clear cornea, and the exit of the needle is at the other side of the trabeculectomy site in clear cornea. The needle passes three-quarter depth through the cornea. Next, impale the conjunctiva near its lip from the underside so that the needle exits from the surface of the conjunctiva. The nylon then passes over the surface of the conjunctiva, and the needle is then passed from the outside surface of the conjunctiva near its lip (at the other end of the trabeculectomy site) to its undersurface and pulled out from underneath the free edge of the conjunctiva. Then this loop is tied and the knot is rotated slightly so that it is underneath the conjunctival lip. When the knot is properly tied, the conjunctiva will be pulled down over the limbus, and the lip of conjunctiva will cover the knot. Use BSS through the paracentesis site to see if a bleb is created. In patients with scarring who need some filtration, a bleb should be created. In patients who are thought to leak easily, the trabeculectomy is closed watertight and a bleb will probably not be noticed. If there are any potential gaps in the conjunctiva, they should be closed with interrupted 10-0 nylon. This is especially important if MMC is used. If no filtration occurs, then be sure to use the paracentesis site to reduce IOP to the low-teens range. Suture lysis will be required in 24 hours. If IOP is not sustained to at least 10 mm Hg, then additional scleral sutures will likely need to be applied, which will require taking the conjunctiva back down. The rare exception to this is if one expects a high degree of outflow dysfunction in the trabecular meshwork, and a high degree of aqueous production, which will support additional filtration. Sometimes lower pressures will be tolerated if the anterior chamber is very deep and the iris is stiff. In most patients, however, it is best to take the conjunctiva back down and "tighten up" the filtration at the scleral flap if the eye does not hold at least 10 to 15 mm Hg.

How Are Combined Cataract and Trabeculectomy Procedures Planned?

When combining this procedure with cataract surgery, there are two major differences:

1. Make the initial scleral flap incision slightly more anterior than usual to make it easier to perform phacoemulsification. That is, instead of beginning a flap 4 mm posterior to limbus, create the incision 2 to 3 mm posterior to the limbus.

2. After the flap is made and it is time to enter the eye, use a keratome (usually 2.6 mm wide) to enter the anterior chamber underneath the flap. Enter in the same way one would normally during a scleral tunnel type cataract surgery. Usually, the entrance for cataract surgery is slightly more anterior (further into clear cornea) than it is with trabeculectomy. This prevents the iris root from coming up through the incision site during phacoemulsification and aspiration.

After the cataract is removed, viscoelastic is used to fill the capsular bag as well as the anterior chamber. The incision is enlarged to about 3.5 mm and a foldable implant (Acrysoft of other nonsilicone material) is inserted.

Before removing viscoelastic from the eye, finish the trabeculectomy. It may be necessary to use a microsharp blade to make another entrance into the anterior chamber beneath the flap, which is more posterior than the existing cataract entrance, to make it easier to use the scleral punch. When more experience is gained, a single entrance into the anterior chamber (i.e., halfway between the normal cataract entrance and the normal trabeculectomy entrance) can usually be used instead. After the iridotomy and before suturing the flap, use the irrigation/aspiration mode to remove the viscoelastic. Because the temporal clear cornea approach is so much easier for cataract surgery, many surgeons are performing each procedure separately.

What Is the Postoperative Care for Patients After Filtration Surgery?

- Apply cycloplegics.
- Apply topical steroid/antibiotic ointment
- Avoid subconjunctival injections, especially when MMC was used. Leaks can develop through needle tracks.
- Apply topical beta-blocker if not contraindicated.
- Give Diamox 500 mg sequel to take with supper if not contraindicated.
- Remember a pressure spike is possible with this procedure, especially if no filtration is present initially.
- See the patient 24 hours later and consider suture lysis. Make note of which suture was required to stop leakage, plan to laser that suture first.
- Use Pred Forte 1% q.i.d. and Ocuflox or Ciloxin q.i.d. as needed. This is continued for at least 1 week, at which time the antibiotic is stopped and Pred Forte is continued q.i.d. another week, then tapered off by decreasing it to three times daily for 1 week, then twice daily for 1 week, then once a day for 1 week. If conjunctival inflammation is still present after tapering Pred Forte, then start fluorometholone (FML) 0.1% q.i.d. for one week and then begin tapering again. Any conjunctival sutures causing irritation should be removed at 1 week.
- If combined cataract surgery is done, Pred Forte 1% may be used more aggressively, that is, every hour for the first day, every 2 hours for 48 hours, and then four times a day for 2 weeks, and then taper as above.

How Is Suture Lysis Performed?

- Use a Hoskins lens to magnify the suture and compress the conjunctiva.
- Use the argon laser with a spot size of 100 μm, power of approximately 200 mW, and time of approximately 0.1 seconds.
- Once a suture is cut, see if the bleb increases and IOP drops to the desired level. If minimal effect is achieved, then continue cutting other sutures one by one.
- Recheck patient again in 24 hours to see if additional sutures will need to be cut.
- Usually suturelysis is ineffective after 2 to 4 days. One of the reasons to use Pred Forte 1% every 2 hours is to extend the time that suture lysis may be effective, that is, usually only up to 48 hours, but with aggressive steroids, possibly up to 4 days or more in some patients.

What Are the Complications of Filtration Surgery?

Some degree of cataract formation is very common.[30] Some other possible complications are listed in Table 19–4. The most common complications are related to the IOP being either too low or too high postoperatively.

Table 19–4. Complications of Filtering Surgeries.

Hypotony
Choroidal effusions
Choroidal hemorrhage
Hypotensive maculopathy
Retinal vein occlusion
Retinal detachment
Peripheral anterior synechiae/angle closure
Optic nerve damage (snuff syndrome)
Pressure spike documented
Transient/occult pressure spike suspected (IOP back to normal on postop visit)
Aqueous misdirection/malignant glaucoma
Damage from retrobulbar or peribulbar block
Needle penetration
Increased intraconal or orbital pressure from hemorrhage or excess volume
Dislodged embolus into posterior ciliary artery or central retinal artery
Infection
Blebitis
Endophthalmitis
Anterior segment and corneal problems
Cataract formation
Foreign-body sensation
Dellen formation
Astigmatism
Tearing
Phthisis bulbi

What If the IOP is Too Low?

Low IOP following surgery is due to either a wound leak (Seidel positive) or overfiltration (Seidel negative). Most wound leaks need to be repaired with additional sutures at the site of leakage. With thin conjunctiva that leaks through needle tracks, sometimes a patch graft is required. Occasionally some suture leaks can be handled conservatively by lowering IOP with topicals or Diamox to reduce the flow of aqueous through the leak and then patching to allow scar tissue to close the wound. Cyanoacrylate (superglue) can also be used to patch a leak. These methods, however, are not often successful and may jeopardize the success of the filter. Usually, it is best to return to the operating room and repair the leak with additional sutures.

If IOP is low due to overfiltration, then conservative treatment is given as long as the anterior chamber is well formed, no significant choroidal detachment is present, and there is no sign of hypotensive maculopathy or retinal vein occlusions (Fig. 19–2).

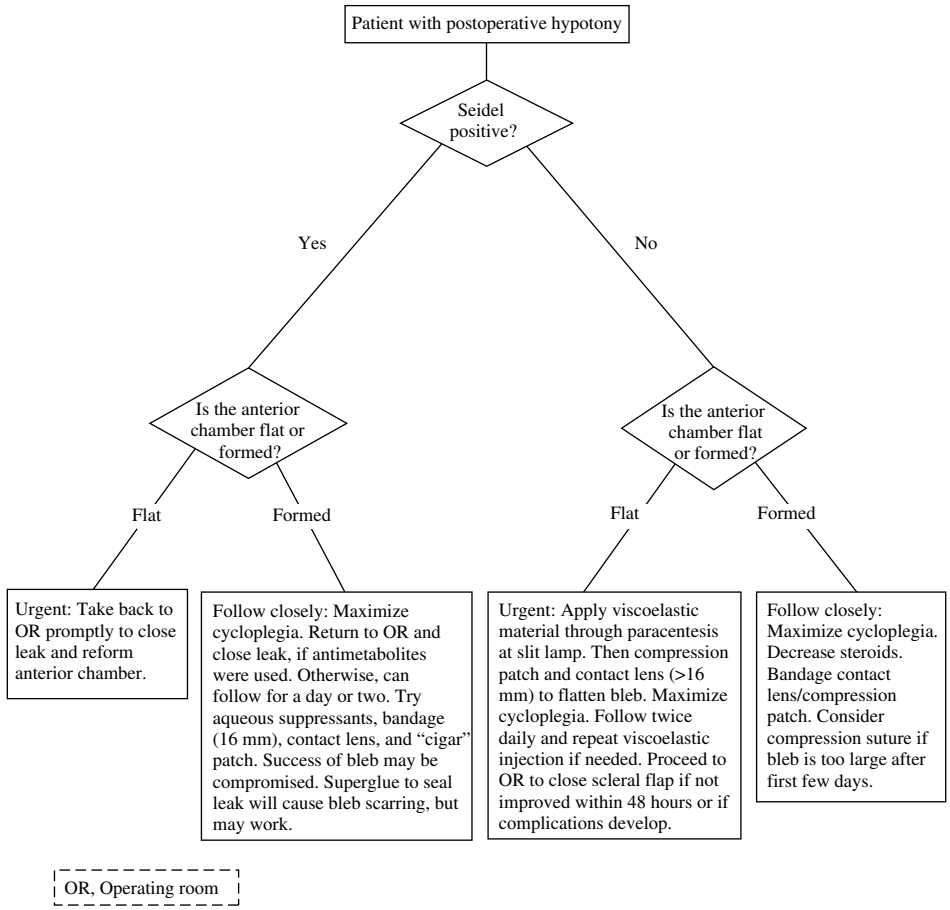

Figure 19–2. Management of postoperative hypotony.

What Is the Conservative Treatment for Hypotony after Filtering Procedures?

Cyclogyl 1% is given four times a day to relax the lens-iris diaphragm and help keep the chamber formed. If the problem is overfiltration (large bleb), a large-diameter contact lens (16 to 18 mm) to reduce the bleb size is helpful, as is tight patching or "cigar" patching (i.e., the placement of an extra "roll" of sterile gauze at the superior lid crease overlying the bleb). Steroids are generally temporarily reduced to allow bleb size contraction. If the anterior chamber begins to shallow and especially if there is any iris–TM touch, then more aggressive steps must be taken.

What Is the More Aggressive Therapy for Hypotony After the Filtration Procedure?

Give Cyclogyl 1% four times a day. Reform the anterior chamber. This can usually be done at the slit lamp by injecting viscoelastic (Ocucoat) through the paracentesis site. If the entrance of the paracentesis has already re-epithelialized, it can be easily opened by using a 27-gauge needle (bevel side up) to poke through the epithelium and reestablish the preexisting paracentesis. Then use the blunt viscoelastic cannula for injection.

- The patient should be checked twice daily and viscoelastic injections can be repeated if necessary.
- If the anterior chamber will not stay formed on its own after 48 hours, then the patient will require a trip back to the operating room to tighten down the scleral flap with more sutures.
- Back in the operating room, be sure to recheck for wound leakage by injecting BSS through the paracentesis site, and applying fluorescein or watching the wound carefully under high magnification to see if there is any leakage. If there is no leakage, but the bleb is very large, this can be handled in two ways. The easiest way is to apply a compression suture. This involves passing an 8-0 nylon suture (spatula needle) through conjunctiva, Tenon's, and episcleral tissue at a point posterior to the bleb, then running the suture across the bleb and passing the needle again through clear cornea at three-quarter depth just central to the limbus and then tying the suture tight to itself to compress the bleb. Extremely large blebs may require two compression sutures running parallel in a similar manner. Horizontal sutures to block posterior flow can also be added. The second way to treat overfiltration is to reopen the conjunctiva and apply more 10-0 nylon sutures to the scleral flap until watertight. This should be checked repeatedly using BSS through the paracentesis to document that the eye can hold the high pressure (greater than 20 mm Hg) before closing the conjunctiva back down. Be sure to close the conjunctiva watertight as well. Do not forget to allow aqueous out through the paracentesis site to titrate pressure back into the low teens at the end of the case. Also, be prepared for the probability of needing suture lysis postoperatively.

If, however, the patient is found to be Seidel positive in the operating room, then a more difficult decision has to be made—whether or not to simply apply

more conjunctival sutures until the patient is Seidel negative, or whether to reopen the conjunctiva, make the scleral flap watertight, and then close the conjunctiva again. Although it is tempting to just apply conjunctival sutures, if the eye has been hypotonous, and especially if choroidals are present, it may be best to go ahead and close down the scleral flap so that one can be certain that postoperative hypotony will be cured. Then the scleral flap sutures can be lasered as needed.

Occasionally, patients with a very thin scleral flap, or poor approximation of the scleral flap, will continue to leak in spite of abundant 10-0 nylon sutures. Sometimes they will even leak through needle tracks (especially with thin scleral flaps). These patients often require either a Tenon's patch graft or a tudoplast graft (preserved pericardium) to close off the leaking scleral fistula. In either case, the tissue is simply sutured to bare sclera to cover the area of leak-

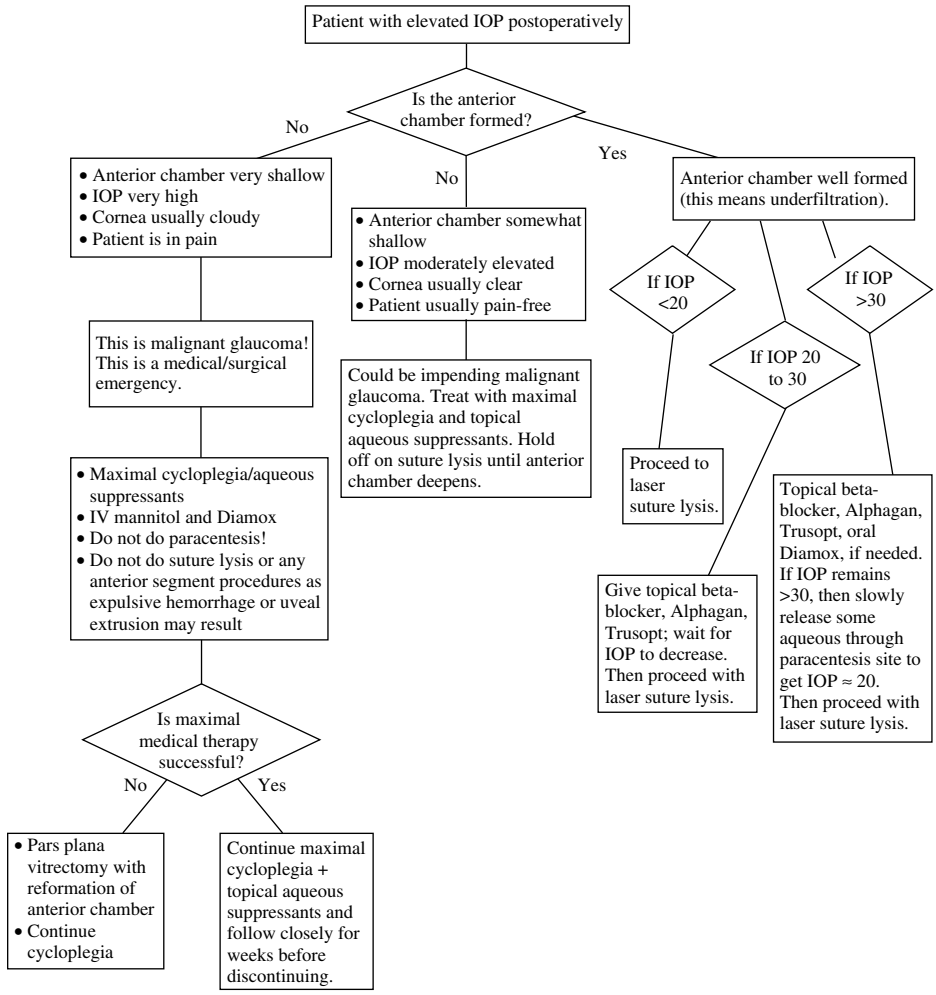

Figure 19–3. Management of a patient with elevated IOP postoperatively.

age. Conjunctiva is then reapproximated and closed. If there is insufficient conjunctival tissue for closure, a conjunctival graft will be needed.

What If the IOP Is Too High During the First Week?

If the anterior chamber is collapsed and the IOP is very high, then the patient may have malignant glaucoma (Fig. 19–3). These patients are treated with maximal dilation and cycloplegia, maximal medical therapy including mannitol, and often still require pars plana vitrectomy. If the anterior chamber is shallow but not collapsed, the patient may have extensive PAS from prolonged hypotony and will require an attempt at angle reconstruction with viscoelastic, as well as surgical reevaluation of the trabeculectomy site.

If the anterior chamber is deep (i.e., no malignant glaucoma) then the patient is underfiltering. Laser suture lysis should be attempted until the desired effect is achieved. If the pressure is very high, then it might be safer to reduce pressure prior to suture lysis. This is attempted medically first, but a 27-gauge needle can be used (bevel up) through the paracentesis site to slowly

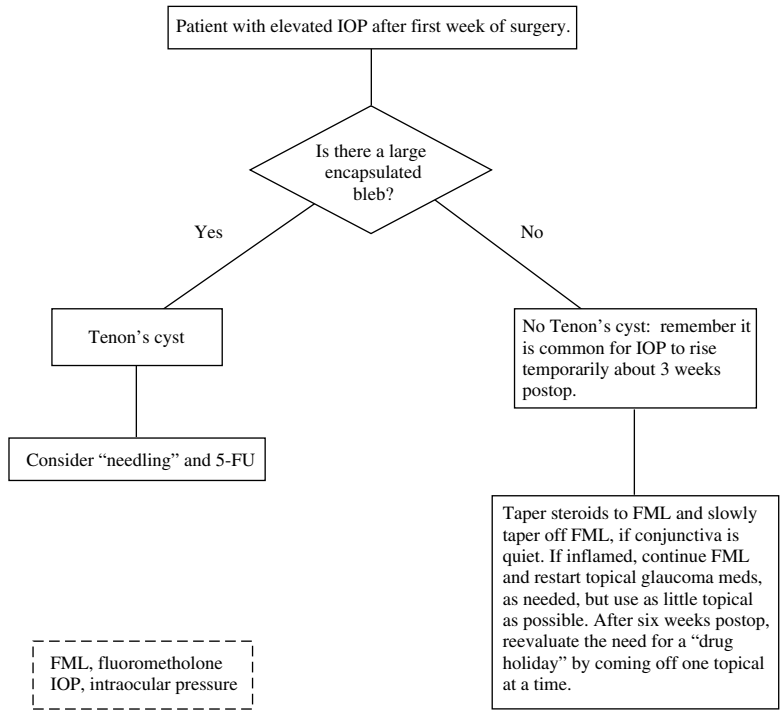

Figure 19–4. Management of a patient with elevated IOP after first week of filtration surgery.

Table 19–5. Needling a Tenon's Cyst

- Apply copious topical anesthesia. Prep and drape the eye, including topical Betadine 25% to rinse out the cul-de-sac. Apply wire rim speculum.
- Use 30-gauge needle to inject lidocaine 2% with epinephrine subconjunctivally.
- Enter subconjunctival space at least 12 mm away from bleb site and inject lidocaine as you advance the needle toward the bleb. This will balloon up the conjunctiva from the needle entrance to the bleb site. It will also provide adequate anesthesia. Then use a 21 to 23-gauge needle through the same track and advance it subconjunctivally and/or sub-Tenon's well into the wall of the Tenon's cyst and as close to the limbus as possible, but at least 4 mm posterior to the limbus. Extreme care must be used to be absolutely certain of not buttonholing through the conjunctiva, especially when working anterior near the limbus. Once the needle is in the Tenon's cyst, rotate the needle or pivot it posteriorly, so that it strips part of its wall posteriorly. If too great a resistance is encountered, then simply poke the needle in and out through the Tenon's cyst several times. Remove the needle and recheck pressure to document filtration. If aggressive aqueous leakage occurs through the needle track, a single 10.0 nylon suture may be required. Usually, however, leakage will stop within minutes on its own. Finally, use a 30-gauge needle to inject 0.5 to 1.0 mL of 5-FU (5 mg/mL). This is not done through the original needle track. Instead, this is usually done on the other side of the bleb. It is not injected into the bleb, but injected at least 20 degrees away from the bleb. After needling the Tenon's cyst, Pred Forte 1% and Ocuflox is restarted. Repeated 5-FU injections every other day for 1 to 2 weeks is helpful.

"burp" aqueous from the anterior chamber if medical therapy is insufficient or too slow.

How Is Elevated IOP Managed After the First Week?

Consider that the patient may be a steroid responder, and begin tapering steroids (Fig. 19–4). Because most patients only need conjunctival treatment rather than intraocular treatment, it is reasonable to change from Pred Fort 1% to FML 0.1% rather early postoperatively. If a Tenon's cyst is developing, and pressure is inadequately controlled with medication, then proceed with needling of the bleb and subconjunctival 5-FU injection near, but not into, the bleb (Table 19–5).

What About Cycloablative Procedures?

These procedures (Table 19–2) are only indicated if all other avenues fail. They reduce IOP by destroying the ciliary body and consequently decreasing the production of aqueous humor. Various types of laser therapies and a cryo procedure are available (Table 19–2). The former more commonly are associated with fewer complications than the latter (see Chapter 22).

In transpupillary (direct) laser cyclophotocoagulation, more controlled destruction of the ciliary epithelium is possible as compared to transscleral laser procedure.[42] Most patients require retro- or peribulbar anesthesia for comfort during this surgery. The 3 and 9 o'clock meridians are avoided to pre-

vent damage to the long posterior ciliary arteries. Laser energy parameters are variable and depend on the nature of the laser material. Complications may also be minimized by treating 270 degrees or less of the ciliary epithelium. The effect on IOP may be dramatic, though many patients require repeat treatments. Most (60 to 70%) end up with pressures of 22 mm Hg or lower.[42–44] Complications include pain, hemorrhage, reduced visual acuity, uveitis, and phthisis bulbi.

Uram[45] introduced endoscopic cyclophotocoagulation in the treatment of glaucoma. He reported a 57% decrease in IOP in patients undergoing combined cataract and glaucoma surgeries

Future Considerations

As previously mentioned, nonpenetrating trabeculectomies and adaptations of shunt devices will be important future considerations. The nonpenetrating trabeculectomies especially sound promising and may become a more common form of glaucoma surgery in the future.

Endoscopic laser cyclodestructive procedures may gain popularity, especially in combined cataract cases as technology advances. Even still the "traditional" guarded trabeculectomy should increase in frequency as the population ages. Planned postoperative suture lysis should also increase in frequency as the benefits of this modification become better known.

Acknowledgments

In that this chapter is mostly a compilation of what I have learned from others, I would like to thank all of those who came before. In particular, I thank my mentors: Dr. Thom Zimmerman, Dr. George Nardin, Dr. Bernard Schwartz, and Dr. M. Bruce Shields.

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◆ 20 ◆

Management of Cataract and Glaucoma

Artemios S. Kandarakis

Definition

What Variables Need to be Considered in Management of Cataract and Glaucoma?

The management of a patient with visually significant cataract and glaucoma poses a clinical challenge for an ophthalmologist. The variables to consider are the patient's age, stage of glaucomatous damage, status of the control of glaucoma, the patient's general health, ability to pay for treatments, noncompliance, and family or social support.

Epidemiology and Importance

Has There Been an Increase or Decrease of Cataract and Glaucoma Over the Years?

Although there are no large studies on the rate of incidence of age-related cataract and glaucoma, it is reasonable to assume that with the increase in the world's older population, there would be an increase in the number of cataract and glaucoma patients as well. Kahn et al,[1] studying the Framingham population, found that among 2,477 subjects aged 52 to 85, the prevalence of senile cataract was 15.5% and that of open-angle glaucoma was 3.3%. More recently, Rahmani et al,[2] studying the Baltimore Eye Survey population of 40 years of age or older, found that the prevalence of cataract was 35.3% and that of glaucoma 4.7%. Similarly, Singh et al,[3] in a total of 903 persons above 50 years of age from Maharashtra, India, found the prevalence of cataract to be 40.4% and that of glaucoma to be 3.1%.

Clinical Pathways in Glaucoma. Edited by Zimmerman and Kooner.
Thieme Medical Publishers, Inc., New York © 2001.

The 5-year incidence of age-related cataract from the Framingham Eye Study ranged from 1% at the age of 55 to 15% at the age of 75.[4] Klein et al[5] estimated the incidence of cataract in the Beaver Dam Eye Study population by taking into account the prevalence of cataract at a baseline examination conducted between 1988 and 1990 and again at the follow-up examination held between 1993 and 1995. They found that incipient nuclear cataract occurred in 13.1%, cortical cataract in 8.0%, and posterior subcapsular cataract in 3.4%. The cumulative incidence of nuclear cataract increased from 2.9% in persons aged 43 to 54 years at baseline to 40.0% in those aged 75 years or older. For cortical cataract, the corresponding values were 1.9% and 21.8% and for posterior subcapsular cataract, 1.4% and 7.3%, respectively.

In Europe, Dielemans et al[6] in the Rotterdam Study concluded that the overall prevalence of primary open-angle glaucoma (POAG) in 3,062 participants over 55 years of age was 1.1%.

What Are the Demographic Characteristics of Patients with Cataract and Glaucoma?

It has been confirmed that the older the individual, the greater the prevalence of cataract and glaucoma.[7,8] Hiller et al,[7] in the National Health and Nutrition Examination Survey (NHANES), found that the risk of cataract at age 70 is 13-fold higher than that at age 50. Klein et al[8] noted in the Beaver Dam Eye Study that the prevalence of glaucoma increased from 0.9% at ages 43 to 54 to 4.7% at age 75 or more. In England, Das et al[9] found that, under the age of 60, Asians had a 30% prevalence of age-related cataract compared to 3% in Europeans, and 78% compared to 54% at age 60 and over. In another detailed study, Mitchell et al[10] examined the prevalence and demographics of age-related cataract in an urban population of Australia. They reported that nuclear cataract involved 51.7% of the population (53.5% of women and 49.7% of men) and was found in 17.6% of persons less than 55 years of age, 34.2% of persons aged 55 to 64 years, 61.8% of persons aged 65 to 74 years, 87.3% of persons aged 75 to 84 years, and 89.6% of persons aged 85 years or older. They also reported that cortical opacities were found in 23.8% of the population (25.9% of women and 21.1% of men) and specifically in 4.4% of individuals less than 55 years of age, 13.1% of those aged 55 to 64 years, 28.4% of those aged 65 to 74 years, 46.7% of those aged 75 to 84 years, and 55.8% of those aged 85 years or older. Finally posterior subcapsular cataracts were seen in 6.3% of the population (6.2% of women and 6.5% of men) and were found in 2.7% of persons less than 55 years of age, 3.8% of those aged 55 to 64 years of age, 6.5% of those aged 65 to 74 years, 11.7% of those aged 75 to 84 years, and 19.8% of people aged 85 year or older. Women are affected slightly more than men are, and this excess in prevalence is mainly due to a higher risk of cortical cataracts.[7,10,11] Mitchell et al[10] also found that the rates of cortical cataracts were higher in women than men in each age group and the age-adjusted prevalence of advanced cortical cataract was significantly higher in women compared with men—relative prevalence 1.21 [95% confidence interval (CI) 1.08 to 1.36]. In the Beaver Dam Eye Study, Klein et al[11] found that women had more cortical opacities than men ($p < .002$).

Dielemans et al[6] reported that age-specific prevalence figures of POAG in the Netherlands increased from 0.2% (95% CI : 0.16, 0.24) in the age group of 55 to

59 years to 3.3% (95% CI : 2.57, 4.04) in the age group of 85 to 89 years. Men had a more than three times higher risk of having primary open-angle glaucoma than women (odds ratio, 3.6). Tuck and Crick,[12] studying the age distribution of POAG in England, found that the prevalence for age 40 to 89 years was 1.2%, rising from 0.2% for those in their 40s to 4.3% for those in their 80s.

Using data from the NHANES, Hiller et al[13] found that cortical and nuclear cataracts were more commonly associated with blacks than whites (relative risk of cortical cataracts 3.5 and of nuclear cataracts 1.8 for blacks versus whites). Blacks have a prevalence of POAG three or four times higher than that of whites.[14,15] There is probably a wide variation of geographic distribution of age-related cataract. In Punjab, India, the prevalence of senile cataract was found to be 15.3% among 1,269 persons aged 30 years and older with a prevalence of 1% for ages 30 to 49 and 67% for ages 70 and older.[16] In the Tibet Eye Study (2,665 participants) the prevalence of senile cataract among persons aged 20 to 32 years was 0.2% and among persons aged 40 or more was 11.8%. The authors attributed these findings to the high altitude (4,000 meters) because this prevalence was 60% higher than the prevalence of a similar, previously conducted study in Shunyi County, China, with an altitude of only 50 meters.[17] However, Brilliant et al[18] also found that cataract prevalence was negatively correlated with altitude in 873 residents of Nepal, reporting a 2.7 times lower prevalence at sites over 1,000 meters than at sites of 185 meters or less ($r = -.0533$, $p < .0001$).

Are There Any Social and Economic Factors Associated with Cataracts and Glaucoma?

Klein et al[19] found that less education was significantly associated with nuclear and cortical cataract, whereas lower income was significantly associated with cortical and posterior subcapsular cataract ($p < .05$). Hiller et al[13] found in the NHANES study that less education was associated only with cortical cataract [realtive risk (RR) = 1.8 for less than 9 years of schooling vs. college], whereas posterior subcapsular cataracts were associated with diabetes (RR = 6.6 for diabetes present vs. diabetes absent) and high systolic blood pressure (RR = 2.2 for 160 mm Hg vs. 120 mm Hg). Positive correlation between cataract prevalence and sunlight ($p < .0001$) was observed by Brilliant et al.[18] Taylor et al[20] examined 838 fishermen at Chesapeake Bay and found that high cumulative levels of ultraviolet B (UVB) exposure significantly increased the risk of cortical cataract (regression coefficient, 0.70; $p = .04$) and that fishermen with cortical lens opacities had a 21% higher average annual exposure to UVB (t-test, 2.23, $p = .03$). In a series of 351 cataract patients operated in Oulu, Finland, Lumme and Laatikainen[21] found that 30% of them lived alone at home, 62% lived with some other person, and 8% were in institutions. Another study has found that anterior subcapsular cataract was significantly ($p = .001$) more prevalent (26%) in participants with schizophrenia than controls (0.2%). [22]

Are There Any Personal Habits That Predispose Patients to Cataract and Glaucoma?

Evaluation of 4,926 participants in the Beaver Dam Eye Study revealed a relationship between cigarette smoking and lens opacities.[23] Specifically, it was found that the frequency of nuclear sclerosis increased with cigarette smoking in

both sexes. For men the odds ratio (OR) was 1.09 (CI = 1.05, 1.14) and for women, the OR was 1.09 (CI = 1.04, 1.16). It was also found that the frequencies of posterior subcapsular cataract (PSC) also increased in both sexes with smoking. The OR was 1.06 (CI = 0.98, 1.14) for women and 1.05 (CI = 1.00, 1.11) for men.

Recently there have been suggestions that good nutrition with antioxidant supplements may have protective association against cataract. Jacques et al[24] investigated the antioxidant status of 112 individuals aged 40 to 70 years, and found that subjects with high levels of at least two of the three vitamins (vitamin E, vitamin C, and carotenoids), are at reduced risk of cataract (OR, 0.2). Similar findings of dietary intake of riboflavin, vitamins C and E, and carotene as well as intake of niacin, thiamin, and iron support a protective effect against cortical, nuclear, and mixed cataract (OR 0.40, 0.48, 0.56, respectively).[25]

Drug intake may also play a role in cataract formation. The association of steroid intake with the PSC is well established. In the Lens Opacities Case-Control Study of 1,380 participants, it was found that oral steroid therapy increased the risk of PSC (OR, 5.83).[25] In the Blue Mountains Eye Study[26] the hypothesis that aspirin protects against cataract formation was not supported because aspirin users for more than 10 years had higher prevalence of PSC than did 40 nonusers (p = .02). In the same study, antihypertensive medications, cholesterol-lowering drugs, and allopurinol were not associated with any type of cataract, whereas the use of antimalarial drug meracrine was associated with PSC (OR, 3.56; 95% CI = 1.56, 8.13) and the use of phenothiazines with nuclear cataract (OR, 2.18; CI = 1.01, 4.74). In a recent study, McCarty et al[22] found that the distribution of the age-related cataract was similar across all users of psychotropic medications (diazepams, butyrophenols, tricyclic antidepressants, and monoamine oxidase inhibitors), with the exception of users of phenothiazines in whom cortical cataract was statistically lower (p = .047).

What Is the Magnitude of the Economic Cost of Cataract and Glaucoma?

Cataract is a major health problem; it is the leading cause of blindness worldwide.[27] It is estimated that more than 1 million cataract surgeries are performed annually in the United States.[28] Steinberg et al[29] analyzed a 5% sample of Medicare beneficiaries who underwent extracapsular cataract extraction (ECCE) between 1982 to 1987. The authors modified the costs by using the 1991 charges allowed by Medicare. It was found that the median charge allowed by Medicare for an uncomplicated routine cataract surgery was approximately $2,500 and that Medicare spent $3.4 billion on cataract-related surgery. In addition, Medicare also spent more than $39 million for preoperative evaluation of nonophthalmologic tests such as cardiac angiograms, and more than $18 million for perioperative medical services. Kobelt et al[30] estimated the direct cost of glaucoma management in a study dealing with 200 glaucoma patients in Germany. They found that during the 2 years of follow-up, 54% of patients had their therapy changed at least once. Mean total charge and cost per patient were 815 and 1,274 deutsche marks, respectively. Mean intraocular pressure (IOP) at baseline was 31.2 mm Hg and after 2 years 18.8 mm Hg. IOP at baseline was positively correlated with costs (p <.01), whereas IOP reduction after treatment initiation was negatively correlated with costs (p <.01). The authors

concluded that because frequent treatment change was associated with higher costs, new treatments that control the IOP effectively over time may reduce the cost of patient management.

What Is the Importance of the Management of Cataract and Glaucoma?

There are quite a few options by which the problem can be solved. These options are based on general principles, surgical experience, and individualization of each case. Cataract and glaucoma are, in the majority of cases, diseases of aging. And as population life span increases, the frequency of both conditions in the same age group may increase as well. Also, the chronic use of glaucoma medications that cause miosis, apart from other side effects, may have a cataractogenic effect. Cataract formation is associated with the use of both directly acting miotics (pilocarpine) and indirectly acting anticholinesterase drugs (phospholine iodide).[31] Therefore, glaucoma and cataract not only commonly coexist, but one can influence the management of the other.

On the other hand, the evolution of both cataract and glaucoma surgery of the past 5 to 10 years has been enormous. Modern cataract surgery is now characterized by the reduced incision size of phacoemulsification, the use of foldable intraocular lenses (IOLs),[32] and improved techniques of management of the miotic pupil.[33] Concerning glaucoma surgery, refinement of trabeculectomy by microsurgery, the possibility of less invasion of the conjunctiva, and the adjunctive use of antimetabolites,[34] releasable sutures,[35] and laser suture lysis[36] have all improved the risk/benefit ratio for the glaucoma and cataract patient.

Therefore, ophthalmologists must be prepared to simultaneously manage cataract and glaucoma, taking advantage of all the latest advances for effectively solving this situation.

Diagnosis and Differential Diagnosis

What Factors Need to be Evaluated in a Patient Suffering from Cataract and Glaucoma?

To evaluate a cataract, pupillary dilation is necessary. One can then identify the types of cataracts (nuclear, cortical, subcapsular), the integrity of the zonules, the existence of pseudoexfoliation or posterior synechiae, the degree of pupillary dilation, and the health of macular area. In a case of axial (nuclear) cataract and miosis (either from miotics or from age), pupil dilation may improve a patient's visual acuity to such a degree that a filtering operation may be sufficient. This approach may work better because the patient, after a successful filtering procedure, might be taken off miotics and not subjected to further miosis. In the case of a low-density cortical cataract, a patient may have 20/40 vision and yet experience severe disability and glare in driving under bright sunlight or facing oncoming vehicle headlights. In the case of a posterior subcapsular cataract, one needs to be extra vigilant because vigorous scraping or vacuuming of the calcified opacity may lead to rupture of the posterior capsule. Zonules become fragile with advanced aging and in the presence of pseudoexfoliation. It is important to identify zonular integrity preoperatively so that an appropriate

surgical technique may be planned. The existence of pseudoexfoliation predisposes to inadequate pupillary dilation, fragile zonules, increased postoperative inflammation, and increased risk of capsular tear during anterior capsulotomy.[37,38] Posterior synechiae prevent complete dilation and their lysis may cause postoperative inflammation as well. Finally, an inadequate pupillary dilation may require additional surgical manipulations for adequate visualization (see below, How Is the Miotic Pupil Managed?).

Examination of the macular area is important to determine whether the decrease in visual acuity is due to lens opacification or retinal disease. The macular function can be determined either by laser interferometer or by the potential acuity meter (PAM). Laser interferometry measures potential visual acuity by using either red helium-neon laser light or simple white light and checks a field size of 1.5 to 8 degrees. PAM projects a Snellen chart through a 0.1-mm diameter aperture and checks a field of vision of 6 degrees.[39] The PAM can be used reliably in cases where visual acuity is better than 20/60 and there is mild to moderate glaucomatous damage, whereas it is unreliable if visual acuity is worse than 20/60 and the damage is severe.[40] The prediction of visual outcome is better if PAM can be used in combination with automated perimetry,[41] which estimates not only foveal area (as PAM does) but perifoveal thresholds as well. Both laser interferometry and PAM perform poorly in mature and hypermature cataracts because the patient may not perceive the test objects. The factors to consider for cataract evaluation in patients are outlined in Table 20–1.

Among the important factors for the evaluation of glaucoma are the type of glaucoma, the degree of glaucomatous damage, its progression or stability, the quality of control of IOP, and the number as well as tolerance of antiglaucoma medications. It is important to identify the type of glaucoma as POAG or secondary glaucoma. The latter category may present unique challenges, such as inadequate pupillary dilation and zonule fragility in pseudoexfoliation glaucoma, lens intumescence, and dislocation in traumatic glaucoma, and intraocular inflammation in uveitic glaucomas. There are also some types of glaucoma that might be associated with cataracts, namely pseudoexfoliative glaucoma,[42–44] Fuchs' heterochromic cyclitis,[45] and uveitic glaucoma. Hiller et al,[42] in a population-based survey with an age-adjusted analysis, found positive but no statistically significant association between pseudoexfoliation and senile lens changes (the odds ratios were greater than 1.0, but did not achieve statistical significance). However, Roth and Epstein[43] found that 40% of the patients with unilateral exfoliation had cataracts in that eye, as compared to 5% in the other eye. Lumme and Laatikainen[44] found a 31% prevalence rate of exfoliation

Table 20–1. Important Factors for Cataract Evaluation

Type of cataract
Integrity of zonules
Presence of pseudoexfoliation
Existence of posterior synechiae
Degree of pupillary dilation
Potential visual acuity
Health of macular area

syndrome in 351 patients undergoing cataract surgery by ECCE. Patients with exfoliation syndrome also experienced a fourfold occurrence of vitreous loss during surgery. Cataract surgery in patients with chronic uveitis is a major surgical challenge. The level of inflammation of the eye has to be estimated preoperatively because postoperatively there may be a greater tendency for increased inflammation, fibrin, and synechiae formation, which may lead to an occluded pupil. Also, cystoid macular edema presents a major obstacle to visual rehabilitation after cataract surgery in patients with uveitis, and if a lens implant is to be considered, it must be placed in the capsular bag.[46] The pertinent factors for glaucoma evaluation are outlined in Table 20–2.

There are difficulties in evaluating the severity of glaucomatous optic nerve damage based on fundus examination or by visual fields in patients with lens opacities. Any opacity of the ocular media can cause localized defects or generalized depression of sensitivity.[47] As the lens becomes denser, less light reaches the retina, and therefore, preexisting field defects may appear denser and larger. Although there are programs that compensate for this influence by subtracting the generalized depression to expose localized defects, if any, still the evaluation is not completely precise.[48] When evaluating visual field defects, attention must be paid to the density of the lens, the visual acuity, and the comparison with previous visual fields. Although the Glaucoma Laser Trial[49] has used its own strict criteria, in general, few (two to three) localized defects at the Bjerrum area and/or mild generalized reduction of sensitivity might be considered minimal optic nerve damage. More and denser localized defects might imply moderate damage. Finally, dense paracentral scotomas or those close to fixation are considered severe damage. A miotic pupil can also cause a significant decrease of sensitivity and constriction of the visual field, and it is desirable for the pupils to be at least 2.5 mm before testing.[50]

When visual fields are confusing, the severity of glaucomatous optic nerve damage may be based on the evaluation of the optic nerve head. Important parameters include cup-to-disc ratio, neuroretinal rim pallor, optic disc blood vessels, and evidence of peripapillary atrophy. Although these are arbitrary categories, damage is minimal if the stereoscopic view of the cup-to-disc ratio is less than or equal to 0.6, moderate if the ratio is between 0.7 and 0.8, and severe if it is equal to or more than 0.9. Also, the presence of an acquired pit of the optic nerve[51] or a disc hemorrhage is a finding of rather severe optic nerve damage and sometimes an indication of progress of the disease.[52] Criteria to evaluate the degree of optic nerve damage in a glaucomatous patient with cataract are listed in Table 20–3.

Table 20–2. Important Factors for Glaucoma Evaluation

Type of glaucoma
Degree of optic nerve damage
Control of intraocular pressure (IOP)
Progression of disease process
Number and tolerance of antiglaucoma agents
Compliance by the patient

Table 20–3. Evaluation of the Degree of Optic Nerve Damage in Patients with Cataract and Glaucoma*

Minimal optic nerve damage
Cup-to-disc ratio less or equal to 0.6
Few (2–3) localized defects in the Bjerrum area
Mild generalized reduction of sensitivity
Moderate optic nerve damage
Cup-to-disc ratio 0.7 to less or equal to 0.8
More (> 3), denser, localized defects in the Bjerrum area or centrally
Severe optic nerve damage
Cup-to-disc ratio greater or equal to 0.9
Dense paracentral scotomas
Scotomas close to fixation
Acquired pit of optic nerve

*Note: Optic disc hemorrhage at any stage of optic nerve damage indicates progression of glaucoma.

What Are the Major Concerns About Cataract Surgery on Glaucomatous versus Nonglaucomatous Eyes?

The chronic use of pilocarpine and other parasympathomimetic drugs causes a miotic pupil mostly resistant to dilation. Inadequate pupillary dilation makes phacoemulsification dangerous because of poor red reflex and uncontrolled capsulorhexis. There is a high incidence of posterior capsule rupture.[38] Indeed, in a patient with a small pupil, the edge of the continuous curvilinear capsulorhexis can be lost under the pupillary margin and a tear of radial fashion can reach the lens equator and sometimes can even extend to the posterior capsule.

Also, the chronic use of miotic agents causes a breakdown of the blood–aqueous barrier, resulting in excessive postoperative inflammation.[53] Chen et al[53] compared 20 eyes in which pilocarpine was not administered prior to performing trabeculectomy combined with ECCE and posterior chamber (PC) IOL implantation, with 40 eyes in which pilocarpine was administered prior to undertaking the same procedures. The authors found that the incidence of complications such as pigment deposits, posterior synechiae, IOL displacement, and capture by the iris was significantly higher in the pilocarpine group ($p < .05$).

Finally, the most important immediate concern is that IOP might rise acutely, usually 3 to 24 hours after cataract extraction. This pressure spike can occur not only after ECCE but also following a phacoemulsification.[54–57] Ruiz et al[54] found an average increase in IOP of 12.9 ± 2.7 mm Hg 24 hours after ECCE in normal eyes, with 55% of eyes exceeding 25 mm Hg. Gross et al[56] reported an IOP equal to or greater than 30 mm Hg in 43% of normal eyes following ECCE and in 27% following phacoemulsification, 2 to 3 hours postoperatively. McGuigan et al[55] reported that four (10%) of 40 normal eyes experienced an increase of 7 mm Hg or more in IOP 24 hours following ECCE. Kooner et al[58] reported that 29% of patients had an IOP greater than 23 mm Hg at 24 hours postoperatively. Hopkins et al[57] reported 52.2% of normal eyes having IOP greater than 20 mm Hg and 22.7% showed IOP greater than 30 mm Hg 4 hours after phacoemulsification.

Such an increase can occur more frequently and to higher levels in glaucomatous eyes.[55,59] McGuigan et al[55] found an IOP elevation of 7 mm Hg or more in 23 (62%) of 37 glaucomatous eyes 24 hours following ECCE. Krupin et al[59] reported that 69% of preoperatively medically controlled glaucomatous eyes that underwent ECCE with PC-IOL alone experienced an increase in IOP of 10 mm Hg or more (range 28–60 mm Hg); 77% of these patients had an IOP greater than 25 mm Hg. Also, Vu and Shields[60] reported IOPs greater than 21 mm Hg 24 hours after cataract surgery in 52% of eyes with glaucoma.

This ocular hypertension may be related to trabecular collapse, retained cortical material, pigment release, inflammation, or the use of viscoelastic substances,[61] although it may occur even when this material is adequately removed at the end of surgery.[62] In patients undergoing ECCE, Naeser et al[61] found IOP higher than 26 mm Hg in 43% of normal eyes when using sodium hyaluronate 1% and in only 19% of eyes when balanced salt solution or air was used ($p < .05$). Berson et al[62] found a 65% decrease in outflow facility after instillation of sodium hyaluronate into the anterior chambers of enucleated human eyes. This decrease was sustained even after vigorous irrigation of the anterior chamber was performed either immediately or 3 hours later.

The pressure spike can occur not only after ECCE with manual nucleus expression but also following phacoemulsification.[56,57] Hopkins et al[57] reported 52.2% of normal eyes having IOP greater than 20 mm Hg and 22.7% with IOP greater than 30 mm Hg 4 hours after phacoemulsification.

Healthy optic nerves may tolerate these transient IOP elevations, but in the presence of glaucomatous damage there may be a permanent worsening of damage.[63] Savage et al[63] reported that 9.7% of glaucomatous eyes had deterioration of visual fields after ECCE and PC-IOL implantation.

Treatment and Management

How Is Coexisting Cataract and Glaucoma Managed?

There are three basic surgical alternatives: (1) cataract surgery alone, (2) combined cataract and glaucoma surgery, and (3) glaucoma surgery alone and cataract surgery later (Fig. 20–1).

There is a long-standing debate on the choice of appropriate surgical approaches in these patients. The final decision may be based on some established general rules, the surgeon's experience, and the complexity of the case itself.

There are three major groups in which the above surgical management alternatives may be applied: (1) medically well-controlled glaucomas, (2) uncontrolled glaucomas, and (3) postfiltering cases.

How Is Medically Well-Controlled Glaucoma Managed with or without Argon Laser Trabeculoplasty (ALT)?

This group includes patients who have one common denominator (well-controlled glaucoma) but differ in the magnitude of glaucomatous damage, the type of glaucoma, and the number of medications required. Specifically, this group can be divided in the following subgroups: (1) well-controlled glaucoma

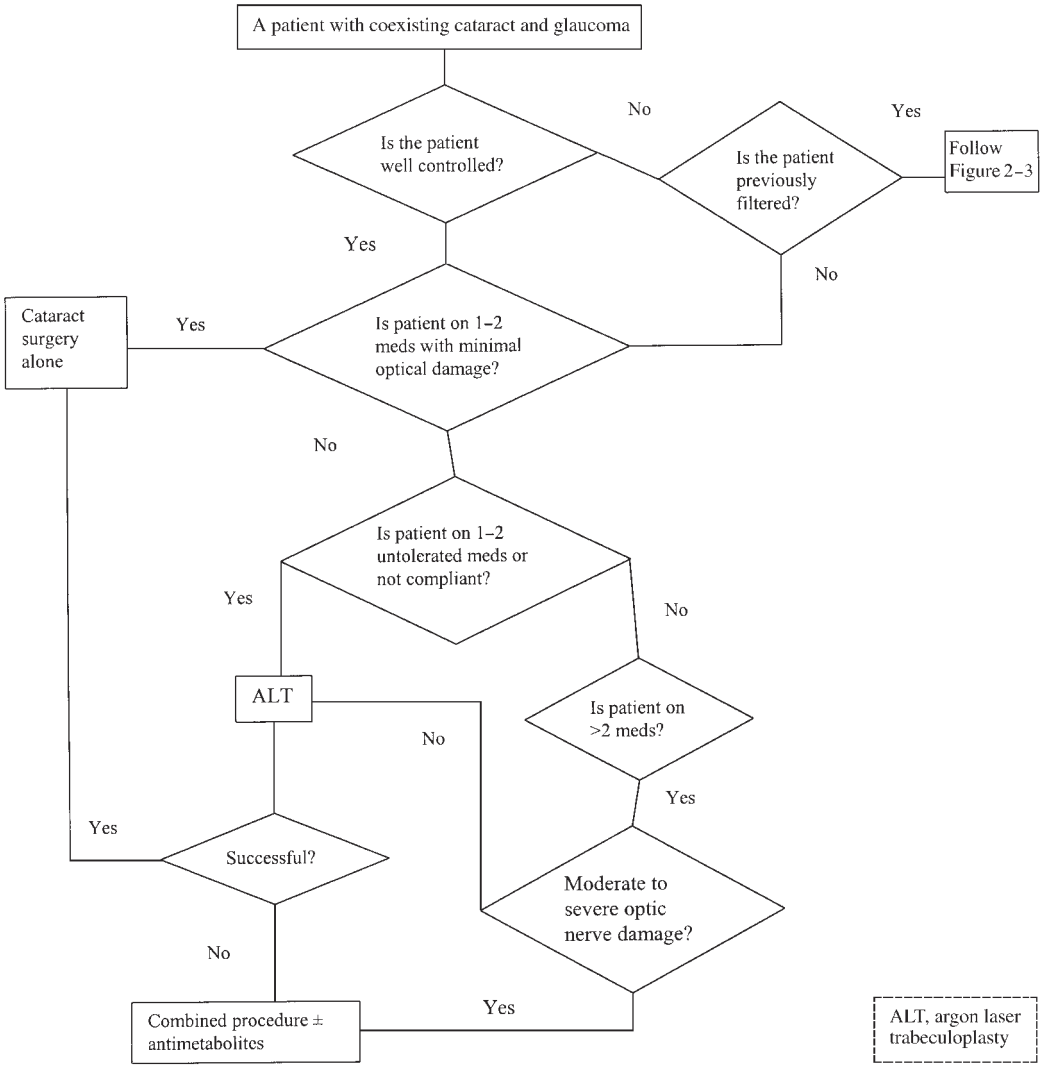

Figure 20–1. Management of the patient with coexisting cataract and glaucoma.

with one or two well-tolerated medications (with or without ALT) and minimal optic nerve damage; (2) well-controlled glaucoma with one or two untolerated medications with minimal optic nerve damage; and (3) well-controlled glaucoma with more than two well-tolerated medications with moderate to severe optic nerve damage.

How Is Well-Controlled Glaucoma Managed If One or Two Well-Tolerated Medications Are Used (with or without ALT) and There Is Minimal Optic Nerve Damage?

The simplest and safest approach to these patients is to perform cataract surgery alone. This decision is based on the fact that a minimally damaged

optic nerve is resistant to the possible postoperative IOP rise.[64] If the glaucoma of these patients is controlled with one or two medications without ALT, then this procedure may be considered preoperatively, especially if a miotic is being used. ALT may help the surgeon in withdrawing the miotic and prevent miotic-induced intraoperative and postoperative complications.

IOP reduction achieved by ALT can be maintained after cataract surgery.[65] Brown et al[65] performed ALT in 25 eyes with a mean prelaser IOP of 23 mm Hg and achieved a mean postlaser IOP of 15.8 mm Hg. After approximately 10 to 11 weeks, all eyes had extracapsular cataract extraction. The mean IOP after an average follow-up of 16 months was 15.1 mm Hg. It is better to perform ALT at least 1 month before the cataract surgery. Four studies have reported an increased rate of encapsulated blebs in eyes with previous ALT,[66–69] although the rate was statistically significant in only two.

ECCE with PC-IOL implantation may sometimes cause a long-term decrease of IOP.[55,70] Steuhl et al[70] attribute this pressure drop to the deepening of the anterior chamber angle after ECCE and PC-IOL implantation. The mean preoperative chamber-angle width in 50 eyes was 28.0 ± 5.6 degrees, whereas the mean postoperative value was 37.4 ± 2.4 degrees, yielding a mean postoperative deepening of the chamber angle of 9.3 ± 4.5 degrees. The chamber-angle quotient was 1.38 ± 0.27.

This IOP reduction may be associated with phacoemulsification as well.[71,72] Kim et al[71] reported 31 medically controlled glaucoma patients who underwent phacoemulsification and PC-IOL implantation with a mean follow-up of 16.4 months. The mean IOP dropped from 18.1 ± 3.1 mm Hg preoperatively to 15.2 ± 2.9 mm Hg postoperatively, and the mean number of antiglaucoma medications dropped from 1.7 preoperatively to 0.7 postoperatively. Similarly, Storr-Paulsen et al[72] reported mean preoperative IOP of 23 mm Hg (range 21–30) and mean postoperative IOP of 16.5 (range 12–18) 12 months after phacoemulsification in medically uncontrolled glaucomatous eyes. This decrease was statistically significant ($p = .005$). The number of medications was decreased from a mean of 2 (range 1–3) preoperatively to 1 (range 0–4) postoperatively, though this decrease was not statistically significant. Small-incision cataract surgery by phacoemulsification also has the added advantage that a filtering procedure may be done at a later date in undisturbed conjunctiva.

How Is Well-Controlled Glaucoma Managed If One or Two Untolerated Medications Are Used with Minimal Optic Nerve Damage?

In this subgroup, although glaucoma may be well-controlled, patients either cannot tolerate the medication or cannot follow the administration schedule (noncompliance). A good option for the management of this situation is to perform an ALT first, to eliminate the need for medications. Later, one may proceed with cataract surgery alone. In case of ALT failure, the surgeon may consider a combined procedure.

Combined cataract extraction and filtration surgery is an effective procedure for patients with visually significant cataract and glaucoma. Small-incision phacoemulsification is preferred over a large-incision ECCE. There are several advantages of a combined procedure. A combined procedure decreases the

magnitude of the early postoperative IOP spike, decreases the number of glaucoma medications, avoids the inconvenience and the cost of a second operation, and provides a rapid visual rehabilitation. Table 20–4 lists the advantages of combined cataract and glaucoma surgery. For more details of combined procedure, see below (How Is Uncontrolled Glaucoma and Cataract Managed?).

How Is Well-Controlled Glaucoma Managed If More Than Two Well-Tolerated Medications Are Used or If There Is Moderate to Severe Optic Nerve Damage?

An optic nerve with this degree of damage might not be able to tolerate postoperative pressure elevations. Elevated IOP may compromise optic nerve head blood flow and result in further permanent and irreversible damage.[59,64] For this subgroup of patients there are several rational alternatives. The surgeon might take advantage of the necessity of cataract surgery and perform a filtering procedure at the same time. This may eliminate or decrease the necessity for antiglaucoma medications, which, although well tolerated, alter the patient's quality of life. In these patients, filtering surgery alone might not be recommended otherwise. However, if the patient has well-controlled glaucoma with good compliance, good tolerance to medical treatment, and minimal optic nerve damage, an equally correct alternative is to perform either cataract surgery alone or an ALT followed by cataract surgery. Those patients with borderline IOP control may also be candidates for combined surgery so as to avoid postoperative spikes.

Whenever in doubt about performing a cataract surgery alone or a combined procedure, the patient's age plays an important role in the final decision. Generally, cataract surgery alone is more appropriate for older patients, whereas combined surgery is better suited for younger ones. Phacoemulsification is preferable, leaving conjunctiva intact for a future filter, if necessary. Optic discs are at greater risk for further damage if the exposure to elevated IOP is of longer duration.

How Is Uncontrolled Glaucoma and Cataract Managed?

In cases of poorly controlled glaucoma and cataract, the goals are the visual rehabilitation of the patient, the avoidance of immediate postoperative IOP rise, and long-term IOP control. This can be achieved theoretically by a combined procedure (see Fig. 20–2).

Until the beginning of the 1990s, ophthalmologists performed a combined procedure by doing an ECCE with PC-IOL implantation and a trabeculectomy.

Table 20–4. Advantages of Combined Cataract and Glaucoma Surgery

Single procedure
Low incidence of early postoperative IOP spikes
Reduced number of antiglaucoma drugs postoperation
Rapid restoration of vision
Less cost

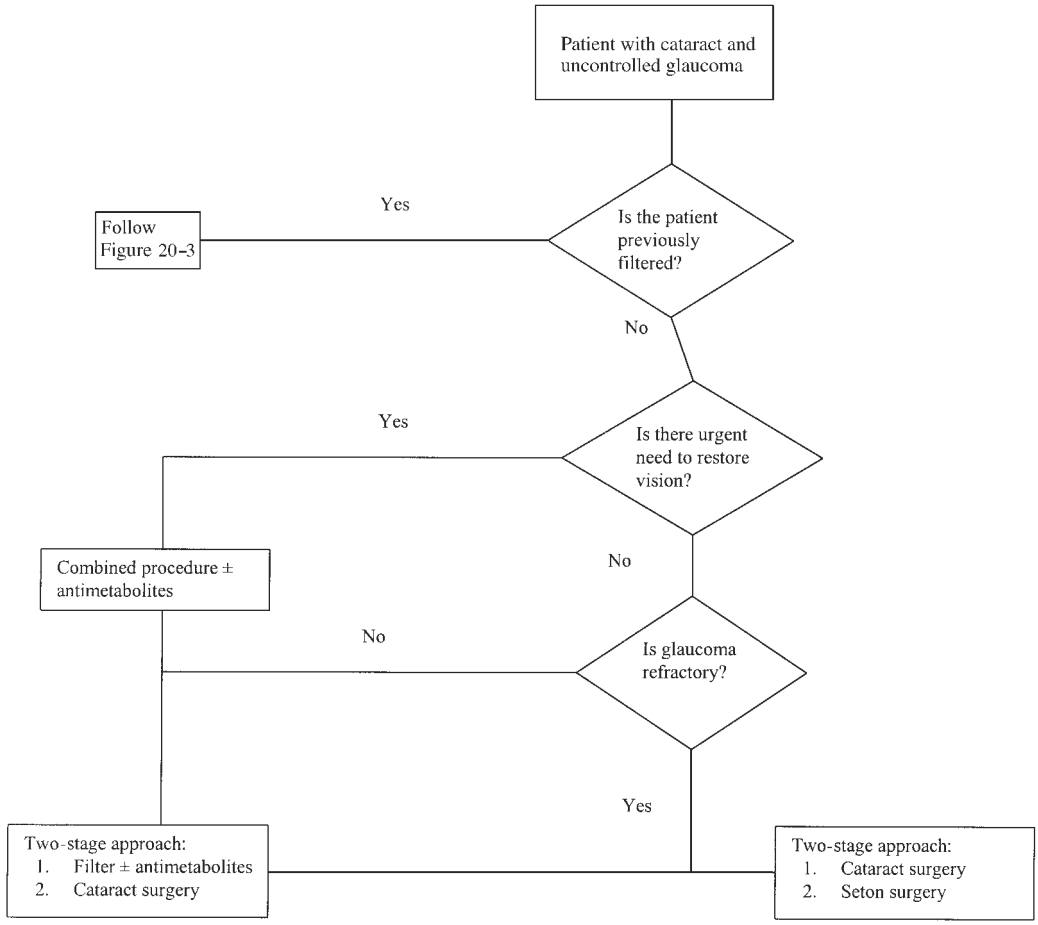

Figure 20–2. Management of patient with cataract and uncontrolled glaucoma.

This combination does not completely eliminate transient increases of IOP, but reduces the frequency and magnitude of this complication. Krupin et al[59] reported an IOP rise of 10 mm Hg or more in 14% of patients and an IOP over 25 mm Hg in 21% on postoperative day 1, following incision ECCE and trabeculectomy. This pressure rise can be related to obstruction of the filtering site by a blood clot, iris, fibrous material, or viscoelastic agent.[73]

Combined surgery also has many complications. Simmons et al[74] reported 27 (36%) of 75 eyes with IOP greater than 30 mmHg and 30 (40%) having a pressure of 7 mm Hg or more above their preoperative level during the first 6 months after large-incision ECCE with IOL implantation combined with trabeculectomy. They also reported detectable filtering blebs in 41% of patients at 2 months and in only 12% at 12 months. Also, hyphema was present in 45% of the cases in the early postoperative period.

Because of the increased rate of complications following a combined ECCE with nuclear expression and filtering procedure, surgeons saved this operation for cases where the glaucoma was poorly controlled. Nowadays, small-incision cataract surgery by phacoemulsification and foldable IOL has replaced the ECCE. Also, adjunct antimetabolites have an increased success rate and increased safety of combined procedures.[75,76]

Small-incision surgery has the advantages of both reduced conjunctival dissection and decreased postoperative inflammation. Therefore, the excessive wound healing and the risk for subsequent bleb failure in combined procedures are reduced.[77,78] The complications of such a modern combined procedure are less and the indications have changed.[77–81] Wishart and Austin[77] compared combined cataract extraction using the extracapsular technique with phacoemulsification, and found that the latter procedure resulted in earlier visual rehabilitation, improved long-term IOP control, and less postoperative astigmatism, as well as less hyphema, fibrous iritis, choroidal detachment, and hypotony. A postoperative pressure rise occurred in 32% of the ECCE-trabeculectomy group and in 23.5% of the phacoemulsification-trabeculectomy group. Shingleton et al[78] reported results from 35 eyes that underwent ECCE, PC-IOL, and trabeculectomy, and 37 eyes that underwent phacoemulsification, PC-IOL, and trabeculectomy. The follow-up was 16 months and the average IOP reduction of the phacoemulsification group was significantly lower (5.0 ± 4.3 mm Hg) than the average IOP reduction of ECCE group (2.9 ± 4.1 mm Hg) (p <.03). The authors did not find significant differences between the groups in postoperative visual acuity and reduction of antiglaucoma drugs.

Wedrich et al[81] compared the efficacy and complication rate between an ECCE-trabeculectomy (ECCE-trab) group and a phacoemulsification-trabeculectomy (Phaco-trab) group. In the latter, the final mean IOP (14.2 ± 3.0 mm Hg vs. 15.5 ± 2.7 mm Hg) was statistically lower (p = .02). Also, in the phaco-trab group, there was a higher percent of patients without medications (82% vs. 65%, p = .07), a lower early postoperative IOP rise greater than 25 mm Hg (2% vs. 18%, p = .009), a lower filtering bleb scarring (8% vs. 63%, p < .0001), and lower total number of complications (63% vs. 87%, p = .006).

Although there is better protection from the early IOP increase, some patients still show IOP spikes after small-incision surgery and trabeculectomy.[57,77,81,82] Hopkins et al[57] reported 13.9% of patients with an IOP between 20 and 30 mm Hg and 5.5% with IOP more than 30 mm Hg, 4 hours after phacoemulsification combined with trabeculectomy, and 20.5% with an IOP between 20 and 30 mm Hg and 4.6% with IOP more than 30 mm Hg on postoperative day 1. These eyes required digital massage alone to lower the pressure without medical therapy.

Similarly, Lyle and Jin[82] found IOP greater than 30 mm Hg in 9.6% of patients having 3-mm incisions and in 6.3% of patients with 6-mm incisions on postoperative day 1 following combined small-incision surgery. The authors do not give any explanation for the percentage disparity of results.

There has been concern about the long-term efficacy of combined procedures. However, as the procedures have evolved with the use of small incisions, long-term success in controlling IOP is improving.[72,83–87] Anders et al[83] compared the results of a no-stitch scleral tunnel phacoemulsification with

standard no-stitch phacoemulsification. They found that 1 year after surgery, the combined procedure group had a decrease of IOP of 7.6 ± 5.5 mm Hg, whereas the standard phacoemulsification group had a decrease of 3.7 ± 4.2 mm Hg. The difference was statistically significant ($p < .001$). Dittmer and Quentin[86] reported a significant decrease in IOP from 21.8 to 14.8 mm Hg following combined phaco-trab with silicone PC-IOL 21.6 weeks postoperatively ($p < .001$). Mamalis et al[87] performed phacoemulsification with PC-IOL and trabeculectomy in 212 eyes, with a follow-up of 26 months. They reported a decrease of IOP from 23.1 mm Hg preoperatively to 15.9 mm Hg postoperatively and of glaucoma medications from 1.85 preoperatively to 0.41 postoperatively. Only 10% had a postoperative IOP greater than 21 mm Hg.

Results of combined phacoemulsification and trabeculectomy with PC-IOL are even better with the use of adjunctive mitomycin C or 5-fluorouracil (5-FU) in selective cases.[75,88] (See below, What Is the Influence of Antimetabolites in a Combined Procedure?)

Another alternative management for uncontrolled glaucoma and cataract is the two-stage approach—filter first and cataract surgery at a later date. Before the evolution of the present combined surgery, the two-stage approach was the procedure of choice in uncontrolled glaucomas, with severely damaged optic nerves, and in cases where there was an immediate threat to vision. Naveh et al[89] reported 40 patients who underwent combined surgery and 38 patients who underwent trabeculectomy alone and followed them for 18 months postoperatively. Pressure levels were significantly lower in the trabeculectomy group (12.8 ± 4.2 mm Hg) than in the combined group (16.5 ± 5.6 mm Hg). However, the technique used was the large-incision ECCE.

Although the evolution of combined surgery with phacoemulsification and the adjunctive use of antimetabolites continues, the success rate is still far lower than trabeculectomy alone.[90] Park et al[90] found a mean IOP reduction of 6.8 ± 5.5 mm Hg in a group of clear-cornea phacoemulsification combined with separate trabeculectomy plus 5-FU, and 10.3 ± 7.6 mm Hg in a group of trabeculectomy alone plus 5-FU. Therefore, trabeculectomy alone is probably still the procedure of choice when there is glaucoma with an immediate threat of vision loss or an inflammatory glaucoma such as Fuchs' heterochromic cyclitis. This approach, however, delays visual rehabilitation for the patient, and both bleb survival and IOP control may be compromised by the subsequent cataract surgery.[91] Cataract surgery should be delayed at least 3 months and ideally for 6 months after a filtering procedure.

What Is the Influence of Antimetabolites in a Combined Procedure?

Antimetabolites may improve the success rate of filtering surgery in glaucoma patients with a poor prognosis.[92,93] However, their efficacy in combined procedures is still controversial.[94,95] Shin et al[94] found a mean IOP of 14.6 ± 4.3 mm Hg in patients with phacoemulsification–PC-IOL–trabeculectomy and mean IOP of 14.7 ± 4.3 mm Hg ($p = .94$) in patients with adjunctive mitomycin C at the last follow-up visit (mean follow-up time 21.0 ± 7.7 months). O'Grady et

al[95] reported no effect of 5-FU and found mean IOP 15.0 ± 5.0 mm Hg in patients with phacoemulsification–PC-IOL–trabeculectomy and 15.4 ± 3.7 mm Hg in patients with adjunctive 5-FU at the last follow-up visit ($p = .45$).

On the other hand, Gandolfi and Vecchi[75] treated one group of uncontrolled glaucoma patients with combined clear cornea phacoemulsification–PC-IOL and separate incision trabeculectomy with 5-FU, and another group without 5-FU as a control. The difference became significant 3 months after surgery and remained so thereafter. At 1 year postsurgery they found that 10 of 12 eyes of the 5-FU group had an IOP less than or equal to 15 mm Hg, whereas in the control group only one of 12 eyes had an IOP less than or equal to 15 mm Hg ($p = .00064$). The IOP range was 10 to 17 mm Hg in the 5-FU group and 14 to 22 mm Hg in the control group.

Derick et al[88] reviewed 42 eyes that underwent phacoemulsification and trabeculectomy with mitomycin C and 42 eyes that had trabeculectomy alone with mitomycin C. At final follow-up at 21.8 ± 6.0 months, the IOP averaged 13.9 ± 5.1 mm Hg in the first group and 12.3 ± 4.7 mm Hg in the second. Shin et al[76] found no statistically significant difference between two groups of nonselected patients with POAG who underwent primary trabeculectomy combined with phacoemulsification and posterior chamber IOL, with or without the adjunctive use of mitomycin C. However, they found that black race, diabetes mellitus, preoperative IOP greater or equal to 20 mm Hg, and more than one preoperative medication were all significant prognostic factors for filtration failure without mitomycin C. They concluded that the intraoperative use of mitomycin C should be selective, limited to patients with one or more of these factors.

Shin et al[96] also reported for the first time that the intraoperative use of 0.5 mg/mL mitomycin C for 3 minutes had an inhibiting effect on posterior capsule opacification after combined surgery.

Although the results with antimetabolites in combined procedures are encouraging, further long-term prospective studies are necessary. In the meantime, adjunctive therapy preferably with mitomycin C seems to be helpful in combined procedures for selective patients with uncontrolled or advanced glaucoma. However, attention should be given to the potential side effects of these agents. For more details of antimetabolites see Chapter 19.

How Is a Cataract Managed Following Filtering Surgery?

The management of a patient with a cataract following filtering surgery depends on the condition of the filter itself. If a patient has a well-functioning filtration procedure and is on no antiglaucoma medications, then the indicated approach is cataract surgery alone (Fig. 20–3).

It is important, if the surgeon's experience allows it, that a phacoemulsification be done. Because postoperative inflammation with this procedure is less, the possibilities for bleb survival are more. Also, small-incision surgery has the advantage of leaving enough space for future filtration if the existing one stops functioning. It is conceivable that clear cornea phacoemulsification is superior, because it leaves even more conjunctiva intact. If phacoemulsification cannot be done, then the approach will be a large-incision ECCE, either limbal (temporal or inferior) or clear corneal with a possibility of large amount of induced astigmatism.

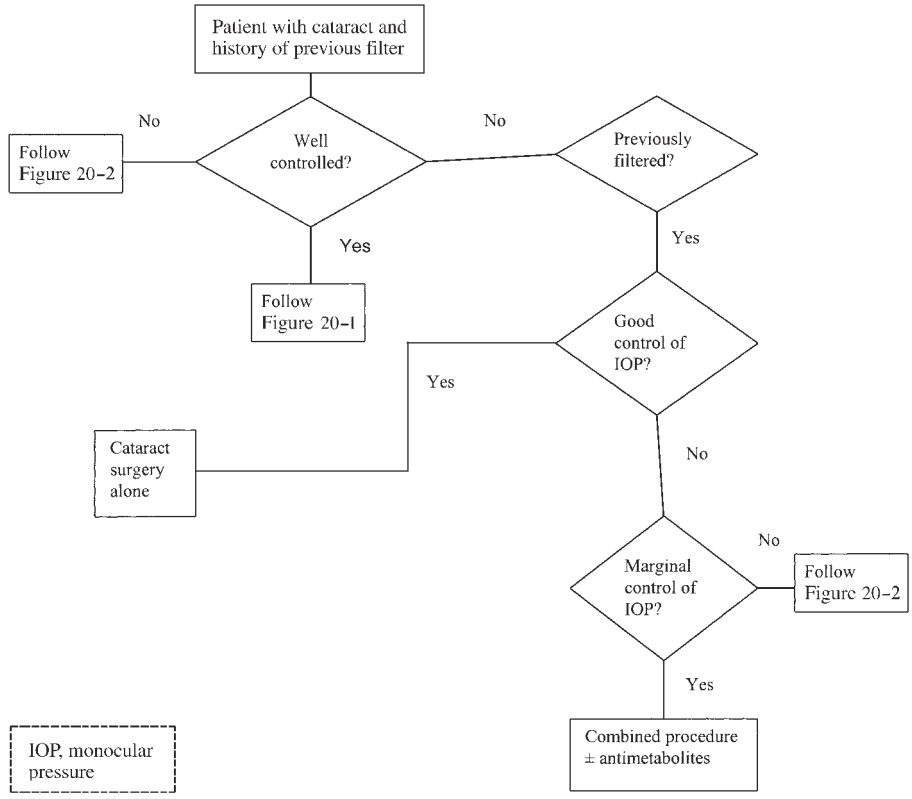

Figure 20–3. Management of the patient with cataract and glaucoma and previous filtering surgery.

Burratto and Ferrari[97] reported 104 eyes with filtering blebs that underwent ECCE and PC-IOL implantation, with good functional results and stable IOP after a follow-up of 8 months. In 33 eyes (32%) they performed ECCE inferiorly and the remaining 71 (68%) eyes underwent phacoemulsification with limbal incision temporally. However, the authors do not mention postoperative astigmatism.

In cases where the filter has completely failed, the postoperative IOP rise may be dangerously high, so a combined procedure is indicated. If the patient has a marginally functioning bleb requiring glaucoma medical therapy, there is still need for prophylaxis against the pressure spike in the immediate postoperative period. On the other hand, cataract surgery of any kind may influence the long-term function of a previous bleb.[98] Possible causes are the postoperative inflammation and the breakdown of the blood–aqueous barrier. In these cases cataract surgery alone will probably cause a complete failure of the marginally functioning bleb.

Shin et al[99] investigated whether previously failed glaucoma filtration surgery is a risk factor for failure of subsequent trabeculectomy combined with cataract surgery. They also compared the role of adjunctive mitomycin C in

repeat trabeculectomy combined with phacoemulsification and a PC-IOL. They found that without mitomycin C, success was significantly less in repeated trabeculectomy combined with phacoemulsification than in a primary trabeculectomy combined with phacoemulsification ($p = .003$). However, by use of mitomycin C intraoperatively, the success rate increased significantly ($p = .02$). The decreased success rate in subsequent trabeculectomy is attributed, according to them and other investigators,[100,101] to the possible change in the composition of the aqueous humor after an intraocular surgery, to breakdown of the blood–aqueous barrier, and possibly to some other unknown reasons. Indeed, it has been shown that aqueous humor from a failed trabeculectomy had a greater chemoattractive activity for ocular fibroblasts than in control subjects.[100] Also, ascorbic acid, which is cytotoxic to Tenon fibroblasts, was in lower concentration in the aqueous humor of eyes that underwent intra-ocular surgery.[101]

So in cases of a marginally functioning or nonfunctioning bleb, a combined cataract extraction preferably by phacoemulsification and probably with the adjunctive use of antimetabolites is indicated.

How Is Refractory Glaucoma and Cataract Managed?

When glaucoma becomes resistant to medical therapy and when filtration surgery, even with the adjunctive use of antimetabolites, fails to control IOP, then the alternatives are either cyclodestructive procedures or tube shunts. These eyes are usually associated with poor prognostic features such as uveitis, aphakia, pseudophakia, neovascularization of the angle, and young age. The cyclodestructive procedures, such as cyclocryotherapy or cyclophotocoagulation, have relatively high rates of phthisis and visual loss.[102] Therefore, in an eye with refractory glaucoma and useful vision, their use is unpredictable and may be sight-threatening. On the other hand, tube shunts are useful alternatives. There is a better success rate and a lower complication rate, but these rates may vary depending on the type of the implant and the type of glaucoma.

Generally, success rates in tube shunts, with respect to control of IOP, range from 58% to 95%, with the lowest success rate in neovascular glaucoma.[103–107] Melamed et al[103] implanted Molteno implants in 41 eyes, and found IOP less than or equal to 18 mm Hg in 32 eyes (78%) after an average of 16 months. Major complications they reported were shallow anterior chamber and hypotony in six eyes (14.6%), vitreous hemorrhage and malignant glaucoma in two eyes (4.9%), and retinal detachment in one eye (2.4%). Fellenbaum et al[104] reported that after implantation of a Krupin valve, IOP was less than 22 mm Hg in 66% 1 year postoperatively. The complications were fibrinous uveitis 24%, shallow or flat anterior chamber 20%, serous choroidal effusion and choroidal hemorrhage 16%, strabismus 12%, obstruction of the slit valve with fibrin 12%, and obstruction of the tube by fibrin or vitreous 8%. Siegner et al,[105] using the Baerveldt implant, reported IOP less than 22 and more than 5 mm Hg in 60.3% 1 year postoperatively. The most common complications were shallow anterior chamber or hypotony 32%, choroidal effusion or hemorrhage 20.4%, corneal decompensation or edema 17.5%, hyphema 14.1%, and tube obstruction 12.6%. Huang et al,[106] in a large series of 159 eyes following Ahmed glaucoma valve implantation, found at 1 year postsurgery IOP between 6 and 21

mm Hg in 87% of eyes and complications in 47%. The most common complications were the obstruction of the tube in 11% and hypotony in 8%. Also, 81% of the eyes were either aphakic or pseudophakic. Only one eye had combined cataract extraction with IOL and valve implantation.

These eyes have had a complicated course and in most cases they had previous cataract surgery. If refractory glaucoma coexists with cataract, it is reasonable to avoid a simultaneous seton insertion and a cataract extraction, avoiding any additional intraoperative or postoperative complications. But patients with extensive subconjunctival scarring may have no choice. A valved seton such as a Krupin or Ahmed is preferable to nonvalved implants. There is a greater need to avoid hypotony and thus prevent complications such as suprachoroidal effusion or suprachoroidal hemorrhage. The surgeon is advised to create an entry site for the seton before proceeding with cataract extraction. Pars plana insertion of the tube may be considered in patients who had prior vitrectomy or are aphakic or pseudophakic. In most cases, it is better to implant the tube shunt separately first, to relieve the optic nerve from the elevated IOP. Then, as soon as the eye is quiet, cataract surgery may follow, preferably by phacoemulsification. Cataract extraction usually does not alter the established function of the tube shunt. It is important to retain an intact posterior capsule or to have a posterior chamber IOL inserted, to avoid vitreous incarceration in the tube.[108]

Finally, in an eye with a cataract and repeatedly failed filters done without the use of antimetabolites, one may consider another filtering procedure with adjunctive use of antimetabolites. Inferior trabeculectomy is also an option, though the patient is at a greater risk for developing bleb infections. Depending on the condition of the patient, the surgeon may proceed to a combined procedure or a cataract surgery alone at a later date.

What Kind of Cataract Surgery Is Preferable for a Glaucoma Patient?

There is no doubt that phacoemulsification is the preferable procedure in most eyes suffering from glaucoma where cataract extraction alone or combined with a filtering procedure is indicated. This is because phacoemulsification provides three important advantages for the glaucomatous eye: smaller incision size, less manipulation of conjunctiva and surrounding tissues, and a reduced amount of postoperative inflammation.

Most glaucomatous eyes are difficult to manage intraoperatively. These patients tend to have hard nuclei, posterior synechiae, small and immobile pupils, and lower endothelial cell counts. Gagnon et al[109] compared the corneal endothelial cell density in 102 patients with glaucoma with that of 52 patients without glaucoma. They found that corneal endothelial cell counts were significantly lower in patients with glaucoma than in controls and in patients receiving three to four glaucoma medications than those receiving one to two ($p < .0001$). It is our impression that in glaucoma patients with long-term use of antiglaucoma medications, a preoperative specular microscopy with endothelial cell count might be helpful and that the surgeon should be aware of possible corneal decompensation.

There is an increased prevalence of cataracts in eyes with pseudoexfoliation.[42–44] Therefore, many patients suffering from pseudoexfoliation glaucoma may present with several characteristics of this disease, such as inadequate dilation before surgery, greater incidence of capsular rupture, fragile and weak zonules, probable phacodonesis, and shallow anterior chamber. Rupture of the posterior capsule, with subsequent vitreous loss and the possibility of inserting an anterior-chamber IOL, creates more problems in glaucomatous than in normal eyes. Kooner et al[110] found an IOP rise of 8 mm Hg above baseline in 25.8% of eyes on the first postoperative day following anterior-chamber secondary implantation, but 3 years postoperatively medical treatment was required in only 11.3% of eyes. Therefore, although phacoemulsification is preferable, the surgeon has to be extremely skillful and experienced before attempting this procedure on a glaucoma patient. It might be much better to perform an ECCE if there is a greater chance of preserving an intact posterior capsule and inserting a PC-IOL in situ, rather than doing a complicated phacoemulsification with broken capsule, vitreous loss, vitreous in the anterior chamber, and a possibility of an anterior-chamber IOL. Almost all difficulties may be managed effectively by an experienced phaco surgeon. Poor dilation can be dealt with by following advanced small-pupil techniques, extremely hard nuclei can be dealt with by chopping techniques, and weak zonules can be dealt with by endocapsular rings. (For details of small pupil techniques, see below, How Is the Miotic Pupil Managed?) However, an experienced surgeon always assesses the risk/benefit ratio for each patient. That means that during the preoperative evaluation, he should formulate a plan that can be changed accordingly intraoperatively, adjusting to the needs of a particular patient.

If the surgeon decides to perform a combined phacoemulsification and trabeculectomy, this can be done with either a one-site or two-site approach. The one-site approach refers to the procedure in which the filter and the phaco are done through the same opening (usually at the superior corneoscleral limbus). On the other hand, the two-site operation is the one in which filter and phaco are performed at two different places. More surgeons who prefer the latter approach perform a clear cornea phaco temporally and a trabeculectomy superiorly.

Wyse et al[111] used mitomycin C and compared the one-site and the two-site approaches and found that IOP reduction was not significantly different (p = .129). However, in a follow-up more than 3 months postoperatively, the percentage of eyes on glaucoma medication was significantly greater (p = .026) in the one-site group (55%) compared with the two-site group (15%), and the former group required significantly (p = .030) more glaucoma medications (0.8 ± 0.9) than did the latter group (0.2 ± 0.6). The possible explanation is that the two-site approach involves less manipulation of the conjunctiva and sclera in the trabeculectomy area. The surgeon is also able to manipulate each surgical site independent of the other in the postoperative period. On the other hand, digital message would be contraindicated in a two-site patient if the corneal wound were not sutured.

Another dilemma for the surgeon is whether the conjunctival flap should be limbal- or fornix-based in a combined procedure. There are advantages and disadvantages of the two approaches. A fornix-based conjunctival flap is easier

to dissect and close, and has better exposure of the wound, and has less chances for buttonholing the conjunctiva, but there may be difficulty in locating the sources of bleeding, there is increased incidence of wound leakage, and the wound is near the trabeculectomy site. A limbal-based flap requires more time, but the wound is away from the trabeculectomy site, is more watertight, and thus is ideal for antimetabolite use. Simmons et al[74] found no difference between limbal-based and fornix-based conjunctival flaps in combined trabeculectomy and ECCE, except a statistically significant difference in the frequency of postoperative hyphema (30% in fornix-based vs. 71% in limbal-based).

Murchison and Shields[112] also found no differences in the two groups with respect to long-term pressure control, visual acuity, and complications. The only difference was the fact that IOP was greater than 30 mm Hg at postoperative days 1 and 2 in only one patient (4%) in the limbal-based group, compared to three patients (14%) in the fornix-based group. Stewart et al[113] studied prospectively the results of limbal- versus fornix-based flaps in patients with combined trabeculectomy and phacoemulsification and found no significant differences at 6 months postoperatively in the level of IOP, number of medication, or complications. Recently Lemon et al[114] have also reported no significant differences in postoperative mean IOP, mean number of medications, and visual acuity between limbal-based versus fornix-based conjunctival flaps in 69 patients with POAG who underwent trabeculectomy combined with phacoemulsification and IOL implantation with adjunctive use of mitomycin C. But there was a significantly higher incidence of postoperative hypotony with wound leak, in the limbal-based group ($p = .019$). Authors believe that this might be related to the excessive conjunctival manipulation that was necessary during cataract surgery because they had not found such a difference in a previous study on primary trabeculectomy and adjunctive mitomycin C with the same closure technique.[115] The excessive conjunctival manipulation was responsible for inadvertent conjunctival wound defects that were not evident intraoperatively, but were leaking postoperatively leading to hypotony. In summary, it seems that there are no significant differences between limbal- and fornix-based conjunctival flap approaches.

How Is the Miotic Pupil Managed?

The miotic pupil is a common finding in glaucomatous eyes. There are several reasons for this troublesome situation. First, although there are many new antiglaucoma medications available, many patients still are under long-term miotic treatment. Second, elderly patients may have age-related miosis. Although in young people dilation is full, quick, and brisk, in the elderly it is usually slow and incomplete. Third, many eyes have developed posterior synechiae because fibrin, which is present in the aqueous due to a disturbed blood–aqueous barrier after miotic use, may produce iris adhesions to the lens. Fourth, pseudoexfoliation is a common finding, according to reports from Europe and Japan.[116,117] In pseudoexfoliation, the pupil is atonic and does not dilate well.[37] Also, inadequate pupillary dilation may occur during ocular surgery due to iris manipulation.

Adequate dilation is a prerequisite for a safe procedure whether planning an ECCE or phacoemulsification. A miotic pupil that does not respond to mydriatics can make cataract surgery extremely difficult and unsafe.[38] Guzek et al,[38] evaluating 1,000 ECCEs, found that decreased pupil size was the only statistically significant risk factor for vitreous loss (p = .0002). Also, even a well-dilated pupil may become constricted during surgery due to iris manipulations. For this reason, surgeons use 0.5 mL of epinephrine 1:1,000 in the infusion bottle to maintain adequate dilation or to achieve further dilation in eyes with borderline mydriasis.

Pupil enlargement can be achieved in different ways. The simplest way to open a fixed pupil is to break any posterior synechiae by first injecting viscoelastic agent in the anterior chamber and then breaking the adhesions with an iris spatula. Miller and Keener[118] developed a procedure of stretching the iris by using a Graether collar button (Storz, St. Louis, MO) or any kind of a "push-pull" iris manipulator and lens positioning hook. The Graether collar button engages the pupil at the 6 o'clock position and pushes it down toward the limbus, while the lens hook engages the pupil at the 12 o'clock position and pulls it up to the limbus. Then the lens hook is inserted through a limbal stab incision at 3 o'clock position and it pulls the iris toward the limbus, while the Graether collar button manipulator stretches toward the 9 o'clock position. By using this stretch pupilloplasty technique, an additional 2 to 3 mm of dilation is achieved. Some pupils become atonic after this procedure.

Another way to manage a small pupil is to create a sector iridectomy through a prior peripheral iridectomy. This opens the pupil superiorly but multiple small sphincterotomies inferiorly may be necessary. Sector iridectomy can be repaired at the end of the procedure with 10-0 polypropylene (Prolene) sutures.[119] This method, although good in ECCE, has been abandoned by phaco surgeons. Large-sector iridectomy usually creates excessive postoperative inflammation and posterior synechiae on the IOL. Also, during phacoemulsification the cut edges of the iris tend to be aspirated in the tip of the phacoemulsification handpiece or the irrigation-aspiration probe. If the patient is elderly or has posterior segment problems, it is acceptable to keep iridectomy unsutured and open for better view of the fundus. However, it may be cosmetically unacceptable. Fine and Masket[33] have devised a system with a preplaced inferior iris suture and an inferior sphincterotomy to facilitate phacoemulsification. After breaking the synechiae, they use a 10-0 polypropylene suture on a straight needle that penetrates the inferotemporal limbus, proceeds through the inferior iris sphincter, and exits from the inferonasal limbus. Then they perform an inferior sphincterotomy followed by a limbal puncture at 6 o'clock, by which they remove both suture ends from the anterior chamber with a microhook. After completing phacoemulsification and implantation of a PC-IOL, the suture will be tied to close the sphincterotomy. If the surgeon decides to suture the iris, 10-0 or 11-0 polypropylene is the most appropriate suture material to use for iris repairing because it provides more permanent support than nylon.

Fine and Masket[33] have also described another method that consists of multiple partial sphincterotomies after lysing any synechiae with a cyclodialysis spatula. The snips are about 0.50 to 0.75 mm long. These sphincterotomies can be done by using the Rappasso scissors. After their completion, the anterior

chamber is further deepened with a viscoelastic material, resulting in pupil dilation of 6.00 mm in diameter. For more dilation, a Lester hook can be used too slowly stretch the pupil at each sphincterotomy site toward the iris root. The authors claim that postoperatively the pupil has relatively normal diameter, is easily dilated, and has a normal light reaction.

Another alternative is the use of de Juan flexible iris retractors[120] made by Grieshaber (Schaffhausen, Switzerland). The retractor consists of a flexible hook made of nylon material and a Silastic slide. A viscoelastic agent should be used to deepen the anterior chamber and any synechiae should be lysed. The manufacturer claims that the retractors are strong enough to break even firmly adherent synechiae, yet flexible enough to prevent damage to the lens capsule. Four retractors are necessary and are easily placed through a self-sealing stab incision at a limbal site. They are adjusted to the appropriate position and tension and fixed with a flexible Silastic slide. At the end of the procedure, they can easily be unhooked from the iris and removed. The end of the hook will bend and slip out of the self-sealing incision. Additional time is required for hook insertion, and sometimes excessive pupillary stretching results in sphincter tears and subsequently atonic pupils. Entry into the anterior chamber should be at an oblique angle for better stretching of the pupil. A vertical entry, for example, will result in tenting of the iris and causing difficulties with phacoemulsification.

There are several pupil dilators also available. They are made of different materials—silicone, hydrogel, or polymethylmethacrylate (PMMA). Morcher (Stuttgart, Germany) type 5 S is a semicircular elastic PMMA ring, with an overall length of 7.5 mm, and with a 0.6-mm groove in which the pupillary edge enters. It provides a dilation of approximately 7.0 mm and it can be used in any type of corneal or limbal incision. It does not need additional incisions and, after removal at the end of surgery, intracameral acetylcholine may provide a fast and relatively normal reaction of the pupil. Pupil dilators should be used only with phacoemulsification and not with ECCE because the nucleus cannot be delivered through a fixed and nonflexible ring opening.

Finally, capsulorhexis and phacoemulsification can be done under a miotic pupil by using a viscoelastic agent and a Kuglen hook to lift and move iris. This procedure does require experience and the surgeon's ambidexterity. The small-pupil techniques are listed in Table 20–5.

Table 20–5. Techniques to Manage Small Pupil

Epinephrine (0.5 mL of 1:1,000 in a 500-cc infusion bottle)
Viscoelastic agents
Breaking posterior synechiae
Stretch pupilloplasty technique
Iris retractors
Multiple fine sphincterotomies
Hook and capsulorhexis technique
Pupil dilators
Keyhole iridectomy

Future Considerations

What Are the Future Considerations in Cataract and Glaucoma Management?

Although there are definite indications for the three options of management of cataract and glaucoma, namely cataract alone, combined surgery, and two-stage procedure, they constantly change due to continuing evolution and refinement of surgical techniques and the great variations in patients. The ideal procedure still does not exist, and the surgeon has to digest and combine the advances in optics, physics, physiology, pathology, and pharmacology.

There is a need for determining the best concentration and exposure time for antimetabolites. Belyea et al[121] studied the results of combined phacoemulsification, lens implantation, and mitomycin C trabeculectomy procedure. They found that although there was excellent IOP control, a surprisingly high rate of progressive diffuse visual field loss was found. There were also two late endophthalmitis cases. The possible influence of mitomycin C in the above complications has to be clarified in further studies.

An interesting new alternative to filtering glaucoma surgery was reported by Jacobi et al[122] in pseudoexfoliation glaucoma cases. They performed bimanual trabecular aspiration of pseudoexfoliation material in 42 eyes combined with ECCE or phacoemulsification. The aspiration was performed by using an aspirator with a tip of 400 μm in diameter and angled at 45 degrees to comply with the anatomic configuration of the anterior chamber angle. Following the entrance of the irrigation probe into the irrigation chamber, the aspirator was introduced through a limbal paracentesis and was pushed forward carefully in the opposite chamber angle and directed against the trabeculum. Under careful tip-tissue contact, and without visualization, suction pressure between 100 and 200 mm Hg was applied for 2 to 3 minutes. The same was repeated for the contralateral side of the chamber angle. The main advantage of trabecular aspiration over a standard filtering operation is that it increases outflow facility along the normal pathway. The procedure seems to be safe, promising, and efficacious in decreasing IOP, but a prospective, randomized multicenter study is necessary.

Recently, Teekhasaenee and Ritch[123] reported results of combined phacoemulsification, PC-IOL implantation, and goniosynechialysis (GSL) in 52 eyes suffering from cataract and chronic angle-closure glaucoma with peripheral anterior synechiae (PAS) of less than 6 months' duration. After completion of phacoemulsification and insertion of a PC-IOL, GSL was performed by using a blunt Swan knife under Barkan goniolens visualization. The mean extent of PAS was reduced from 310 to 60 degrees, and the IOP was reduced to less than 20 mm Hg in 47 eyes (90.4%) without medication. This procedure seems promising and the future will show its efficacy.

Foldable IOLs are now widely used in cataract surgery. However, there has been no clear evidence that IOL material has a clinically significant effect on the postoperative course of a combined cataract and glaucoma procedure. Kosmin et al[85] compared silicone versus PMMA lenses in phacoemulsification combined with trabeculectomy and found that 1 year after surgery, IOP control was attained without medication in 80.0% in the silicone group and 76.7% in the PMMA group (p = 1.00), with no statistically significant early postoperative

complications. Hollick et al[124] reported that polyacrylic lenses were associated with a significant difference ($p = .0001$) of less posterior capsule opacification (10%) than silicone (40%) and PMMA lenses (56%) 3 years after cataract surgery. Again, a prospective randomized multicenter study, comparing all parameters of different foldable IOL materials, is necessary.

New research is targeting the search for materials to fill the capsular bag after cataract surgery, which would undergo hardening by polymerization from light exposure. Hettlich et al[125] performed in vitro experiments on enucleated pig eyes and in vivo on rabbit eyes. However, they recorded temperatures as high as 45.1°C during the polymerization process. Therefore, refilling materials with better physical properties need to be developed.

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Management of Glaucoma in Pregnancy

Brian R. Sullivan

Introduction

This topic deals with the diagnostic and treatment concerns evolving from the occurrence of primary or secondary glaucoma in women of reproductive age, especially during the natal and postnatal periods.

Definition

Why Is Pregnancy an Issue of Concern in Glaucoma?

Therapeutic dilemmas may arise during the management of glaucoma in women of childbearing age due to the risks of impaired fertility, maternal and fetal toxicity, teratogenicity, and harmful effects on the nursing infant. Treatment of glaucoma in pregnant and nursing women should be approached with caution. This problem may become more common in the future as more women are choosing to defer childbearing until later in life.

Epidemiology and Importance

How Common Is Glaucoma in Pregnant Women?

The coexistence of glaucoma and pregnancy is an unusual clinical problem, and glaucoma is rarely initially diagnosed during pregnancy. Although the fertility period extends from the second to the fifth decades of life, the prevalence of glaucoma in this population of women is undefined. The clinical variability of

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glaucomatous disorders adds to the difficulty in determining confusion over prevalence data in this group of young females. The term *glaucoma* refers not to one entity, but to a large group of diverse disorders with the common features of ocular hypertension, visual field loss, and optic neuropathy. In addition,there is increasing evidence that primary open-angle glaucoma (POAG), the most common glaucoma diagnosis, may be a genetically heterogeneous collection of clinically similar or even indistinguishable diseases. The general demographic and socioeconomic characteristics of POAG and other forms of glaucoma are discussed elsewhere in this text, but such data should be interpreted cautiously in addressing glaucoma issues in women of reproductive age. Unfortunately, there is remarkably little pregnancy-specific epidemiologic data available regarding the various glaucomas, but some conclusions can be drawn from existing knowledge of glaucoma and pregnancy demographics.

Because POAG is associated with aging and the elderly, the disease is generally considered uncommon in pregnancy. The prevalence of POAG increases with age,[1] and it is very uncommon under age 40. Of one series of young glaucoma patients between ages 10 and 35, only 25% had the diagnosis of POAG.[2] However, POAG occurring in younger patients has been observed to be associated with high initial intraocular pressure (IOP) and may represent a more severe form of the disease.[3] Therefore, POAG that is coincident to the condition of pregnancy, although rare, may require relatively aggressive management.

Has the Incidence of Glaucoma in Pregnancy Increased in Recent Years?

Currently there are no data available supporting an increasing coincidence of pregnancy and glaucoma. It might be suggested that the clinical scenario of POAG during pregnancy could become more common in association with increasing childbearing in middle adulthood. There is a national trend of increase of births in women who have delayed starting their families until later in their careers,[4] but the incidence of glaucoma has not yet been studied in this population of mothers.

What Type of Glaucoma Occurs During Pregnancy?

In the general population, POAG is the most common form of glaucoma, but, for the reasons discussed above, this observation cannot be extrapolated when considering the population of young women. It has been suggested that juvenile open-angle glaucoma is the predominant type of glaucoma occurring among women of childbearing potential.[5] Glaucoma that occurs during adolescence and young adulthood often is also the result of underlying ocular or systemic disease, and in many cases abnormalities of the anterior chamber angle can be identified. Therefore, when referring to women of childbearing age, the developmental and secondary glaucomas are of increasing significance, particularly those associated with inflammatory ocular diseases, chronic steroid use, prior intraocular surgery, and/or trauma. It should be noted that there are no reported cases of pregnancy-induced open-angle glaucoma, and there are no forms of secondary glaucoma unique to pregnancy. Narrow-angle glaucoma may worsen with advancing pregnancy complicated by preeclampsia,[6] but this

relationship has not been clearly established by published findings. Acute-angle-closure glaucoma has been reported in one case to be precipitated by labor, perhaps triggered by emotional and physical stress at delivery.[7] However, acute angle closure more typically occurs past the fifth and sixth decades of life, and this problem is rare in young females.

Is There a Relationship Between Glaucoma and Pregnancy-Induced Hypertension in Preeclampsia or Eclampsia?

The positive correlation between ocular hypertension and systemic hypertension[8–10] is an issue worthy of consideration in addressing glaucoma in pregnancy because the incidence of pregnancy-induced or -aggravated hypertension has been reported to be as high as 5 to 10% of a general population of pregnant women, and over 20% in nulliparous women.[4] It has been observed by Qureshi et al[11] that ocular tensions of third trimester hypertensive women were significantly higher than tensions of third trimester nonhypertensives. In this report, a total of 200 women were studied, including 40 nonpregnant controls. A difference of mean IOP of 0.6 mm Hg, measured by Goldmann applanation, was found between late pregnancy normotensives and hypertensives, and, although small, this difference was found to be statistically significant. However, this study contradicted earlier work by Phillips and Gore[12] demonstrating no significant difference of mean IOP between third trimester hypertensive and nonhypertensive women. In their report, hand-held Perkins applanation tensions were obtained in a total of 97 women including 25 nonpregnant normotensive controls. Mean late pregnancy IOP was 12.1 and 12.4 mm Hg among normotensives and hypertensives, respectively, and the small difference was not found to be statistically significant. A finding of pregnancy-induced lowering of IOP in the third trimester was observed in both hypertensive and nonhypertensive groups in both of the above studies. In both reports the drop was found to be statistically significant, and the mean decrease in IOP ranged between 2.0 and 2.7 mm Hg (13–18%). This interesting phenomenon is further discussed below.

Does Pregnancy-Induced Diabetes Mellitus Affect IOP?

An increased prevalence of POAG and ocular hypertension in general populations of diabetics has also been suggested,[8,13–15] but this relationship has not been demonstrated in pregnancy-induced diabetes mellitus.

Could Additional Epidemiologic Data Improve Patient Care?

The currently available information is of insufficient quality to estimate incidences of various types of glaucoma in women during reproductive years. It can only be stated that glaucoma during pregnancy is considered uncommon. As childbearing at older maternal age becomes more frequent, it is not known if the coincidence of glaucoma and pregnancy is increasing accordingly. Advanced age has not yet been identified as a risk factor for glaucoma during the condition of pregnancy, and the significance of other glaucoma risk factors

in pregnancy is unclear. IOP normally decreases during pregnancy, and it is unlikely that systemic hypertension during pregnancy affects IOP in a clinically significant manner. Further epidemiologic study could enable better glaucoma management decisions for the patient who is pregnant or at risk of pregnancy. Determination of pregnancy-specific prevalences, risks, and prognostic factors would be useful for improved glaucoma assessment, and possibly in avoiding unnecessary and potentially hazardous treatment.

Diagnosis and Differential Diagnosis

How Are Various Glaucomas Diagnosed in the Pregnant Patient?

Assessment of glaucoma in the pregnant patient involves application of the same clinical principles as in any patient with suspected glaucoma. Such evaluation should include appropriate classification and diagnosis of the type of glaucoma, and determination of the stage of the disease by optic nerve examination and perimetric analysis. Potential risk factors must be identified including IOP, refractive error, other ocular disease, age, race, family history, and systemic disease. In the young female patient, a particular effort should be made to elicit histories of prior glaucoma or ocular hypertension, nonglaucomatous ocular disease, and eye trauma. A review of records from previous eye examinations is important to characterize the duration and progression of the disorder. Medical history and review of systems are also pertinent, particularly in cases of secondary glaucoma.

Features of the glaucoma exam are discussed in more detail elsewhere in this text, and, although younger and healthier, the pregnant woman should be evaluated equally as thoroughly as the more typical elderly glaucoma patient. Careful examination of pupils, external features, anterior segment, and posterior segment should be performed with particular attention to intraocular tension, gonioscopy, and optic nerve appearance. The optic nerve exam should be detailed to include characteristics of cupping, color, contour, vascular changes, and disc hemorrhages. Any asymmetric findings should be carefully noted.

Classification of glaucoma in any patient is based on the underlying mechanisms leading to the common pathways of optic neuropathy and visual field loss. Discrimination should be made between open- and closed-angle glaucoma with attention to identifying any underlying ocular, systemic, or genetic disorders. In dealing with glaucoma in younger ages associated with pregnancy, one must be mindful that the relative occurrences of developmental glaucomas and secondary glaucomas are likely to be higher than that of POAG in women of childbearing years.[2] In cases of suspected or known secondary glaucoma, it is important to document all orbital and ocular abnormalities, especially inflammatory, posttraumatic, and neovascular findings. Pregnant or potentially pregnant patients with uveitis of unknown etiology should always undergo extensive systemic evaluation using laboratory and other ancillary

studies to rule out identifiable underlying conditions that could threaten the welfare of mother, fetus, or nursing infant.

In Addition to Physical Examination, What Other Studies Are Useful?

Because progressive loss of visual field is a common potential outcome for all forms of glaucoma, visual field testing is the most important adjunctive diagnostic tool in detecting and following the disease. In managing the pregnant glaucoma patient, perimetry remains equally invaluable because it is a safe, sensitive, and noninvasive test. Because various forms of glaucoma do not characteristically worsen at an accelerated rate during pregnancy, it is not usually necessary to obtain serial perimetry data in greater frequency than in the nonpregnant glaucoma patient. Visual field screening during pregnancy may also yield results atypical for glaucoma, and the reported findings have been well discussed in a review of the effects of pregnancy on the eye.[16]

Nonglaucomatous visual field loss in pregnancy has been described in older literature as early as 1923,[17–19] but contemporary reports are surprisingly lacking. The reported abnormalities include the findings of bitemporal or concentric field loss, usually detected near term. Other studies failed to verify such findings.[19] Such changes, when discovered, are usually asymptomatic and usually resolve shortly after delivery.[16] Initial investigators suggested that the field defects might be attributed to physiologic enlargement of the pituitary gland during normal pregnancy. However, in pregnancy, the degree of enlargement of an otherwise normal pituitary gland is insufficient to affect the chiasm, and visual field abnormalities are not explained by this mechanism.[19] It is recommended, therefore, that any woman who demonstrates unexplained visual field abnormalities during pregnancy should undergo further evaluation for underlying disease affecting the visual sensory system, particularly central nervous system lesions.

Other ancillary tests, which may also be helpful in evaluating glaucoma disorders, include optic nerve photography, and computerized disc and nerve fiber layer analysis.

Does Pregnancy Have Any Effect on IOP?

The interpretation of IOP during pregnancy warrants additional discussion. It has been demonstrated that in all trimesters of pregnancy, intraocular tensions are lower than in nonpregnant controls. The ophthalmology literature consistently describes a trend of decreasing IOP with advancing pregnancy, especially in the second and third trimesters.[12,16,20,21] Using applanation tonometry, Phillips and Gore[12] and Qureshi et al[11] recorded IOP data in totals of 97 and 200 women, respectively. Both reported third trimester drops in IOP ranging between 13% and 18% compared to nonpregnant controls, with a lesser degree of decrease of mean IOP in hypertensive patients.[12] Additionally, the finding of decreased IOP has been observed to persist for several months after delivery.[22] Wilke[23] observed reduced episcleral venous pressure in pregnancy by measur-

ing repeated applanation tensions in 20 pregnant women in the third trimester and comparing to those of 20 nonpregnant controls. It was suggested that decreased episcleral venous pressure contributes to the ocular hypotensive effect of pregnancy, as a result of the observed systemic phenomenon of lowering peripheral vascular resistance.[23,24] Patterson and Miller[25] performed repeated tonography throughout pregnancy on seven healthy primigravid women, and found an initial steep increase of outflow facility with peaks at approximately 20 and 26 weeks. The observed percentage increase of the coefficient of outflow ranged between 9% and 133%. The facility of outflow values declined near parturation, with further decreases in the postpartum period to near-normal values.

There is substantial evidence of a hormonal mechanism[20] for pregnancy-induced lowering of IOP. Systemic progesterone, which gradually rises endogenously throughout pregnancy, has been noted to decrease IOP in glaucoma patients.[26,27] Relaxin, another hormone that increases during pregnancy, has been shown to reduce IOP and increase outflow facility in glaucoma subjects.[20] A third hormone of pregnancy, β-human chorionic gonadotropin (β-hCG), reduces IOP by suppressing aqueous production.[28]

How Does Pregnancy Affect the Glaucoma Patient?

The above observations have several important implications for the pregnant glaucoma patient. First, there has been a general impression that preexisting glaucoma improves during pregnancy.[16,20,29] Women with the existing diagnosis of glaucoma may require fewer or no glaucoma medications for adequate IOP control while pregnant. Second, the IOP-reducing effect of pregnancy may cause normal or near-normal tension measurements when the pregnant woman with glaucoma is initially evaluated, potentially masking the disorder. This phenomenon could result in missed diagnosis or underestimation of the severity of the glaucoma, especially in those cases in which earlier clinical information is unavailable. Third, because the IOP-lowering benefit diminishes slowly after delivery, women with glaucoma need careful monitoring of IOP control in the postpartum months. Glaucoma suspects should be followed similarly because ocular hypertension may appear or worsen.

Treatment and Management

Is She Pregnant? Does She Think She Might be Pregnant?

Whenever considering any treatment of a woman of childbearing age, it is important to be mindful of the possibilities that she could be pregnant or become pregnant during the treatment period. This issue is especially significant in treatment of chronic diseases such as POAG. Failure by any physician to address these possibilities can result in inappropriate management and medicolegal concerns. Specific history taking prior to initiating management is therefore crucial. Female patients do not typically volunteer the possibility of pregnancy during ophthalmic consultation. Questions should specifically

determine the woman's estimated likelihood that she may be pregnant or contemplating future childbearing. The date of the most recent menstrual period should be documented to note any delay or cessation of menses. Current specific method of contraception should also be noted if considering the use of a known or suspected teratogenic agent. The diagnosis of pregnancy may also be inexpensively determined with fairly high accuracy via laboratory pregnancy testing by detection of urine or blood β-hCG. Referral to the patient's primary care physician or obstetrician should be considered if the diagnosis of pregnancy is in question.

Ideally, in treating glaucoma in young women, patients should be counseled prior to conception regarding any known or estimated risks of drug therapy. However, in practice, medications taken chronically are usually not discontinued prior to the time pregnancy is diagnosed, and exposure occurs well beyond the period of conception and critical organogenesis. Therefore, the prescribing ophthalmologist should be vigilant of any teratogenic or toxic potential of all medications used in managing glaucoma in women of reproductive age, regardless of known or planned pregnancy. Particular caution should be taken in prescribing any medication during a recognized pregnancy, because litigation can result from an adverse outcome despite nonsupporting or contrary scientific evidence for toxicity and teratogenicity. Hence the term "litogen."[30]

How Can It be Determined if Glaucoma Medications Cause Harm During Pregnancy?

Any glaucoma drug that is absorbed systemically should be considered to have the potential to affect the fetus or to be excreted in breast milk. In theory, the biochemical properties of most glaucoma drugs should allow transfer across the placenta without impediment.[31] However, the use of any topical ophthalmic medication is uncommon during pregnancy, and data regarding teratogenic or toxic effects are generally inadequate. Early evidence of human teratogenic effects of a pharmacologic agent arises from clinical case reports, but high-quality epidemiologic studies are necessary to determine meaningful and statistically significant associations between drug exposure and offspring abnormalities.[32] Because the coincidence of glaucoma and pregnancy is uncommon, studies of large human populations are not possible to assess the toxicities of even common glaucoma medications to the fetus or nursing infant. Conversely, agents that are inappropriately "accused" of being human teratogens may also be associated with sparse scientific literature, and the proposed cause-effect relationship should be viewed critically. Those drugs unlikely to pose a human hazard are often not exonerated by scientific support due to insufficient data.[32] It is important for the patient and practitioner to be mindful that pregnancy has inherent risks, and the majority of congenital malformations occur in the absence of drug or chemical exposure.[33]

In counseling patients regarding drugs with insufficient human scientific data involving risks in pregnancy, it may be of some benefit to examine the results of animal tests. Teratogenic studies in laboratory animals are available regarding many glaucoma drugs, but the results cannot always be extrapolated to infer risk in humans.[34] This problem is partly due to the usually high doses used in most animal experiments, resulting in systemic levels incomparably

higher than those resulting from typical dosages of medications used in ophthalmology. Similarly, comparison of data from human experience is difficult because an ophthalmic drug administered topically is generally associated with systemic levels fractional to levels achieved by oral or other routes used for nonophthalmic indications. Much of the useful information regarding adverse reactions in humans arises from case reports and epidemiologic studies generated after a drug has come into general use, but because the coincidence of glaucoma and pregnancy is uncommon, specific data remain sparse despite even widespread use of a glaucoma agent. Unfortunately, premarketing evaluation of drug effects on reproductive function and pregnancy, whether in vitro, in animals, or in humans, is usually inadequate to properly estimate risks of teratogenicity and other toxic effects.[35] Drug testing is intentionally avoided in the specific population of pregnant women.[36]

If there is no human or animal evidence to evaluate potential pregnancy-related hazards of a drug, it is difficult to assess risk at any exposure levels. Patients should be advised that the risk is not known. Sometimes, more knowledge may exist regarding safety of other drugs in the same class of compounds. If the drug has a physical structure or mechanism of action similar to that of a known toxicant or teratogen, then it is reasonable to suspect increased potential for adverse effects, despite the absence of formal evidence. Because patients seek rational guidance from their eye care providers, it is important to disclose the amount and quality of scientific information supporting the advice provided, especially when hazard data is incomplete.

A summary of bioavailability and Food and Drug Administration (FDA) category data of common drugs used in glaucoma treatment are listed in Table 21–1.

What Glaucoma Management Issues Should be Considered for Women During the Reproductive Years?

Recommendations for ophthalmic drug use near or during pregnancy, therefore, evolve from limited available data, with the assumption that eye drops are absorbed systemically via the nasolacrimal duct system and nasal mucosa.[37] The patient and her ophthalmologist must attempt to resolve the dilemma of benefits versus risks on an individual basis. For a young woman with no near-term plans for childbearing, the potential of a drug for impairment of future reproductive capacity must be considered, although usually this risk is unknown. When a woman becomes pregnant or plans pregnancy, the glaucoma management plan should be reassessed. Any nonessential ophthalmic drug should be avoided. Particular attention should be paid to ensure that drugs with known contraindications are not used, with cautious and reserved use of any others. Judgment of the benefit to risk ratio involves weighing the often poorly defined teratogenicity and toxicity risks against the possible visual sequelae resulting from deferral of glaucoma treatment. Women in earlier stages of glaucoma may be able to tolerate short-term moderate elevations of ocular tensions for up to 9 months if glaucoma drugs are temporarily discontinued.

Table 21–1. Common Glaucoma Drugs During Pregnancy and Lactation

Agent	Effect on Placenta	Crosses Placenta	Secreted in Breast Milk	FDA Risk Category
Timolol	Unknown[i]	Yes	Yes[ii]	C[iii]
Levobunolol	Unknown[i]	Yes	Unknown	C
Carteolol	Unknown[i]	Yes[iv]	Yes[iv]	C
Metipranolol	Unknown[i]	Unknown	Unknown	C
Betaxolol	Unknown[i]	Yes	Yes	C
Pilocarpine	Unknown[i]	Unknown	Unknown	C
Carbachol	Unknown[v]	Unknown	Unknown	C
Echothiophate iodide	Unknown[v]	Yes	Unknown	C
Epinephrine	Yes[iv]	Yes	Unknown	C
Dipivifrin	Unknown	Unknown	Unknown	B[vi]
Apraclonidine	Unknown	Unknown	Unknown	C
Brimonidine	Unknown	Yes[iv]	Yes[iv]	B
Dorzolamide	Unknown	Unknown	Yes[iv]	C
Brinzolamide	Unknown	Unknown	Yes[iv]	C
Acetazolamide	Unknown	Unknown	Yes[ii]	C
Methazolamide	Unknown	Unknown	Unknown	C
Prostaglandin $F_{2\alpha}$	Yes	Unknown	Unknown	C
Mannitol	Unknown	Unknown	Unknown	C
Glycerin	Unknown	Yes	Unknown	C
Fluorouracil	Unknown[vii]	Unknown[vii]	Unknown	D[viii]
Mitomycin	Unknown[vii]	Unknown[vii]	Unknown	D

[i] Theoretical effects due to presence of β-receptors in placental tissue. No further data available.
[ii] Classified as a maternal medication usually compatible with breast-feeding by the American Academy of Pediatrics Committee on Drugs.
[iii] Category C: Either (a) studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other) and there are no controlled studies in women; or (b) studies in women and animals are not available.
[iv] Demonstrated in animal only.
[v] Theoretical effects due to presence of cholinergic activity of placental tissue. No further data available.
[vi] Category B: Either (a) animal reproduction studies have not demonstrated fetal risk, but there are no controlled studies in pregnant women; or (b) animal reproduction studies have shown an adverse effect (other than a decrease in fertility) in the first trimester (with no evidence of risk in later trimesters) that was not confirmed in controlled studies in women.
[vii] Teratogenic effects in animals well established. Systemic use during pregnancy contraindicated.
[viii] Category D: There is positive evidence of human fetal risk.

Because of the intrinsic IOP lowering effect of pregnancy itself, the IOP control may be found to be surprisingly stable after withholding medications. If drug therapy is deemed necessary, the safest possible choice should be made, and the medication should be administered in the lowest dose estimated to be effective. Dosage and duration of use should be minimized as much as is consistent with acceptable glaucoma care.[38] Women should be clearly instructed in nasolacrimal occlusion after instillation of eye drops to minimize systemic absorption. It may be necessary to advise against breast-feeding because of theoretical harm from drug distribution into milk, especially if the uses of β-antagonists or carbonic anhydrase inhibitors cannot be withdrawn. Pregnancy also presents an opportunity to consider early use of laser trabeculo-

plasty, iridotomy, and other nonpharmacologic approaches to glaucoma management. As in all cases of glaucoma, those women with late-stage optic nerve cupping or poor IOP control, with risk factors for progression, should be treated more aggressively. Filtration surgery, which could decrease or eliminate dependency on pharmacologic agents, particularly carbonic anhydrase inhibitors, should be considered as an early alternative to medical management in women contemplating pregnancy. Surgical intervention should be strongly considered in advanced glaucoma cases and optimally should be performed well before the onset of pregnancy.[39] However, surgical management, even when considered successful, often does not eliminate dependency on drug therapy for glaucoma.

In summary, the ophthalmologist must consider reproductive issues in decision making and patient counseling for all young women with glaucoma requiring medical treatment. Contemporary methods of glaucoma management should enable good treatment before and during pregnancy with satisfactory perinatal maternal and fetal outcomes, even in advanced cases of glaucoma.

What Is Known About β-Antagonist Use in the Pregnant Glaucoma Patient?

Despite limited maternal-fetal toxicity data, some classes of glaucoma drugs such as beta-blockers are generally thought to be acceptable for use with caution during pregnancy. Concerns over maternal adverse effects of β-antagonists are the same as those in the nonpregnant patient, including the potentials for precipitation or aggravation of obstructive lung disease or heart failure, bradycardia, drowsiness, and interference with diabetic control.[40,41] Such maternal effects are thought to be dose dependent, with the potential for compromise of fetal well-being. There are data showing that atenolol (Tenormin), an oral cardioselective beta-blocker, is associated with a significant increase in intrauterine growth retardation when prescribed from the first trimester,[42] and it has been suggested that other beta-blockers are likely to have the same effect.[41]

Several investigators have shown an abundance of β-adrenergic receptors in human placental tissue,[43–46] even in early gestation.[47] In addition, several of the commonly used ophthalmic β-antagonists are known or suspected to traverse the placenta.[31,48] In an animal model, timolol was observed to prevent the rebound tachycardia normally seen after hypoxia in the fetus.[49] However, the effects, if any, of topical ophthalmic β-antagonists on the placenta or fetus have not been specifically observed. The reported clinical experience with ophthalmic β-antagonists in pregnancy is, overall, somewhat limited despite their widespread use, especially in younger glaucoma patients. Beta-blockers have been anecdotally reported to be relatively safe for use during pregnancy,[50–53] but contraindicated after delivery in nursing mothers.[16,38,54,55] Maternal use of oral β-antagonists near delivery has been associated with persistent and potentially hazardous beta-blockade in the newborn infant.[56–59] Timolol (Timoptic) has been demonstrated to be secreted in breast milk, with milk levels up to six times that of serum after topical ophthalmic use.[54,60] Betaxolol (Betoptic) was also found to be concentrated in breast milk, with a milk/plasma ratio of 3.0.[52] Although the observed milk levels in these cases remained well below

cardioeffective dosages, topical β-antagonists should be prescribed very cautiously during nursing due to the serious and possible lethal side effects of beta-blockade in infants, particularly apnea.[61,62] Though not contraindicated, the use of β-antagonists near delivery should be avoided when possible, and infants exposed in utero should be monitored closely during the first 24 to 48 hours after birth for apnea, bradycardia, and other symptoms. Despite the above concerns, the American Academy of Pediatrics Committee on Drugs has classified timolol as a maternal medication usually compatible with breast-feeding.[63]

Are Miotics Prescribed in Pregnancy?

Ophthalmic use of parasympathomimetic agents has not been demonstrated to be teratogenic in humans, but, although not contraindicated, this class of glaucoma medications should not be used indiscriminately during pregnancy. Consideration could be made in withdrawing miotic use when the woman is near term, due to possible transient effects on the newborn infant. Pilocarpine has been associated with signs mimicking neonatal meningitis, and transient newborn muscular weakness has been observed in association with cholinesterase inhibitor use during pregnancies of mothers treated for myasthenia gravis.[55] Case evidence has been published demonstrating that echothiophate iodide crosses the human placental barrier with apparent inhibition of fetal pseudocholinesterase activity.[64] No clinical complications of mother or infant were noted, but caution was advised by the authors due to unknown fetal hazards. There is also well-documented cholinergic activity of the human placenta, but the functions of these cholinergic components are not yet well understood.[65] Among other suggested roles, the placental cholinergic system has been linked to myometrial and placental prostaglandin release during parturation, release of placental hormones, and regulation of blood flow in placental vessels.[66] It is not known whether ophthalmic cholinergic agonists have any influence on the placenta function and hormonal milieu. Carbachol and pilocarpine have been associated with developmental abnormalities of animal embryos,[67–69] but to date these drugs have not been implicated as human teratogens. Case reports of safe use of miotics during pregnancy and lactation have been described in the ophthalmic literature,[54,70] but caution is warranted due to unknown, perhaps unlikely, placental and fetal effects.

What Information Exists Regarding Pregnancy and the Use of Adrenergic Agents?

Topical drugs in a third class of topical glaucoma medications, the sympathomimetics, are also considered relatively acceptable for use in pregnancy, but reported experience is sparse. First trimester use of ophthalmic epinephrine has been described with no adverse outcome.[54] Epinephrine readily crosses the placenta,[71] but because epinephrine occurs endogenously, it is difficult to distinguish effects of the administered drug from naturally occurring epinephrine. One concern is that epinephrine administration during pregnancy might

decrease uterine perfusion. In a pregnant animal model, a greater than 34% reduction of uterine blood flow was observed after administration of a low dose of epinephrine that did not affect blood pressure.[72] Studies of possible impairment by epinephrine of fetal gas exchange have been conflicting.[73,74] Animal studies have failed to demonstrate harmful fetal effects of dipivefrin (Propine), but human experience is limited, with no controlled studies in pregnant women.[75] Nursing women should be treated with caution because it is not known if topical ophthalmic epinephrine or dipivefrin is significantly secreted into milk.

Experience with α_2-adrenergic agonists is similarly limited. Animal studies have shown no impairment of fertility or fetal harm of brimonidine tartrate (Alphagan), but the drug, in animal models, is known to cross the placenta and is excreted in breast milk.[76] Unlike β-receptors, α-adrenergic receptors are not found on the maternal or fetal sides of the human placenta.[77] There is evidence of an α-adrenergic role in the mechanism and regulation of prolactin secretion,[78] but it is not known if ophthalmic brimonidine use has any significant influence on plasma prolactin levels in animals or humans. Reproductive studies of apraclonidine (Iopidine) in animals have shown no impairment of fertility, but embryocidal effects and maternal toxicity have been observed with high doses during pregnancy.[79] There are no adequate human studies involving either drug in pregnant women. It is recommended that α-adrenergic agonists be used with caution during pregnancy and nursing, weighing unknown potential fetal risks with the value of treatment of the mother.

Have Carbonic Anhydrase Inhibitors Been Used in Pregnancy?

Oral carbonic anhydrase inhibitors are relatively contraindicated during pregnancy and lactation. Acetazolamide (Diamox) and methazolamide (Neptazane) have well-documented teratogenic potential in animals,[80–84] and a case has been reported of an infant with sacrococcygeal teratoma, born to a mother treated with acetazolamide, among other medications, during the first trimester.[85] However, the proposed carcinogenic effect of acetazolamide on the fetus has not been substantiated by other reports, and retrospective studies have suggested no increased human fetal risks.[86,87] Use of acetazolamide after the first trimester has been described in a number of cases without adverse effects.[64,87–89] Two cases of neonatal dehydration and metabolic disturbances have been reported, involving mothers who had been treated near term with acetazolamide.[89,90] Acetazolamide has been shown to be secreted into human breast milk to levels of approximately one-third of maternal plasma concentrations,[91] signifying the potential for infant exposure to the drug. In glaucoma treatment, oral carbonic anhydrase inhibitors should be avoided in nursing women whenever possible, especially in cases of impaired neonatal respiratory, hepatic, or renal function. It should be noted, however, that the American Academy of Pediatrics Committee on Drugs has classified acetazolamide as a maternal medication usually compatible with breast-feeding.[63]

The relative hazards of topical carbonic anhydrase inhibitors are even less clear because systemic drug levels are expected to be somewhat below those of

oral medications. Brinzolamide (Azopt) has been found in milk of lactating rats at concentrations below those of plasma, but it is not known if brinzolamide is excreted into human milk during maternal use.[92] Animal studies showed no adverse developmental or mutagenic potential of oral dorzolamide at 12 to 13 times the human ophthalmic dose, but treatment-related malformations were reported at much higher doses.[93] The limited information suggests some degree of safety of dorzolamide (Trusopt) in the low doses used in ophthalmology. Again, caution must be taken in interpreting data from animal studies and in extrapolating the findings to humans. There are no adequate human studies evaluating adverse effects of topical carbonic anhydrase inhibitors on reproductive capacity or fetal development, and abnormal reactions of nursing infants are not known. Given the limited evidence for safety, it is recommended that topical carbonic anhydrase inhibitors be considered for glaucoma therapy with marked caution during pregnancy, with use limited only to the second and third trimesters. After delivery, options should include decisions to discontinue breast-feeding or to discontinue the drug in the nursing mother. In summary, alternative treatment to oral or topical carbonic anhydrase inhibitor use should generally be sought in managing glaucoma in childbearing women.

Can Pregnant Women be Treated with Prostaglandins for Glaucoma?

Chronic use of prostaglandin agents in the management of glaucoma, particularly POAG, has become increasingly popular in recent years. Human experience with the use of topical prostaglandin analogues in pregnancy is not described. Endogenous prostaglandins appear to have important roles in the reproductive cycle, including both normal and pathologic states, but mechanisms of action remain poorly understood. It is suspected that the vascular abnormalities in preeclampsia may be mediated by prostaglandin effects, and increasing data indicate that prostaglandins play a major role in parturation. Blood and amniotic fluid levels of $PGF_{2\alpha}$ and other prostaglandins are elevated near term and during labor. Therapeutic uses of PGE_2, $PGF_{2\alpha}$, and prostaglandin analogues have been described extensively for the induction of labor and treatment of pregnancy complications.[94] Several such agents have also been used as abortifacients. Obstetrical use of prostaglandins remains limited by the associated side effects and complications, as well as by persistent confusion over their complex mechanisms, despite a large body of clinical data.[94]

Ophthalmic uses of prostaglandin analogues in fertile or pregnant women should be approached cautiously. Latanoprost (Xalatan), a $PGF_{2\alpha}$ analogue, has been observed to have an embryocidal effect in animals at 15 to 80 times the maximal human dose, but no human pregnancy data are available.[95] In mice and rats, $PGF_{2\alpha}$ caused malformations and increased abortion,[96,97] but was not teratogenic in rabbits or hamsters.[98,99] $PGF_{2\alpha}$ is a known potent stimulator of uterine contraction,[100] and it has also been demonstrated to be a vasoconstrictor of the fetoplacental vascular bed,[94] the ductus arteriosus,[101,102] and the fetal pulmonary vessels.[103] Thus, the issue of systemic absorption of prostaglandin analogues raises well-founded concern over

increasing risks of pregnancy complications. It is not known if latanoprost or other prostaglandin analogues reach circulating levels of any clinical significance when administered in topical ophthalmic doses. The biologically active form of latanoprost is rapidly eliminated from human plasma ($t_{1/2}$ = 17 minutes),[95] suggesting perhaps minimal potential effect on the reproductive cycle. However, because of the known bioactivity of prostaglandin drugs in pregnancy, further study is needed to assess the safety of ophthalmic use of this class of drugs. It is this author's recommendation that, until further data are available, latanoprost and other prostaglandin agents be avoided during pregnancy. If an ophthalmic prostaglandin is considered for use due to unacceptable alternatives, careful obstetrical comanagement of the patient is recommended to monitor for maternal-fetal side effects.

Is There a Role for Hyperosmotics in Glaucoma Management During Pregnancy?

Hyperosmotic agents have been used in ophthalmology usually for emergency or short-term treatment of glaucoma. Such drugs are particularly effective in acute angle-closure glaucoma. Despite well-known systemic effects and complications, discussions of potential problems with the use of these agents during pregnancy are nearly absent in the ophthalmic literature. Mannitol induces abortion when instilled in the amniotic cavity, but may result in only diuresis if given intravenously in pregnancy.[104] In rats, intravenous mannitol has been observed to cause hemorrhagic abnormalities of fetal limbs, but malformations were not seen.[105] Administration of hypertonic agents, including mannitol, to pregnant sheep has been observed to cause fluid shifts involving fetal compartments.[106,107] Additional evidence does not suggest any specific teratogenic effects of mannitol. Human pregnancy experience with use of oral hyperosmotic agents such as glycerol (Osmoglyn) and isosorbide (Ismotic) is unavailable. It is known that glycerol is transferred across the placenta in small amounts,[108] but reports of adverse fetal effects cannot be found. Systemic complications of hyperosmotic agents are more likely to occur with intravenous use, and short-term use may be hazardous to the mother and/or fetus. Potential metabolic, renal, and cardiovascular abnormalities may result in direct insult to the fetus or compromise of the fetoplacental circulation. Hyperosmotic agents are thus relatively contraindicated in pregnancy, and any seemingly unavoidable use should be preceded by extensive obstetrics consultation and patient counseling of risks.

What Other Glaucoma Treatment Options Could be Offered to Childbearing Women?

Nonmedical therapies for glaucoma should be considered in women of reproductive age as alternatives to the potential risks associated with glaucoma agents during pregnancy and nursing. The prospect of surgical management can be considered, especially in younger women who are dependent on oral

carbonic anhydrase inhibitors for acceptable IOP control. Ideally, such intervention should occur well prior to the onset of pregnancy,[39] and while the visual prognosis is still good. When medical control becomes inadequate, the ophthalmologist should avoid procrastination of surgery. Delay of glaucoma management due to unexpected pregnancy could perhaps result in further field reduction. It has been suggested that cases of late-stage glaucoma and advanced fixation that threaten visual field loss should receive aggressive management in the antenatal period due to the risk of progression precipitated by the bearing down effect during labor and delivery.[109] In such situations, vaginal operative delivery or cesarean section could be considered in an effort to avoid further late-stage visual field loss.

Laser trabeculoplasty can be an excellent alternative to medical therapy in childbearing women, and the procedure may be safely performed during pregnancy or the postpartem period. Further, the option of argon laser trabeculoplasty (ALT) could be considered early in the management of POAG for women during the reproductive years, with the goal of decreasing or eliminating dependency on medications. Several reports have also described favorable results in support of early filtration surgery in the general population of patients with open-angle glaucoma.[110–113] Young women with glaucoma may also benefit from early surgery, and the issue should be discussed if a patient is planning pregnancy. Intraocular surgery, however, should generally be avoided when possible during an existing pregnancy, because of anesthetic risks and potential difficulties in managing complications. The hazards of antimetabolite use as adjunctive treatment in filtering surgery during pregnancy are also unknown, although fluorouracil and mitomycin C have known teratogenic potential.[5] Trabeculectomy and other forms of filtration surgery, if indicated, usually can be deferred until after delivery, unless, in the practitioner's judgment, severe maternal vision loss is imminent despite maximally tolerated medical therapy. In the rare event of unavoidable surgery, it is this author's recommendation that antimetabolites should not be used during pregnancy and lactation unless further data supporting such use become available (Fig. 21–1).

Future Considerations

Pregnancy after the age of 35 is becoming increasingly common in our society, often because of career issues. Successful pregnancies in cases of advanced maternal age have been enabled by improved fertility and obstetrical care, but the coincidence of glaucoma and pregnancy may be higher during later childbearing years. It is hoped that further research will eventually refine knowledge of glaucoma management in the subpopulation of women during reproductive age and pregnancy. More epidemiologic information would be useful in assessing risks of glaucoma in pregnancy, particularly in identifying those risks of medical treatment. Practitioners have a responsibility for reporting adverse drug reactions, and cumulative case experiences may be helpful in modifying recommendations concerning indicated drug use during pregnancy. The issues of human teratogenicity and maternal toxicity are complex and difficult to address experimentally, and treatment of glaucoma in pregnancy con-

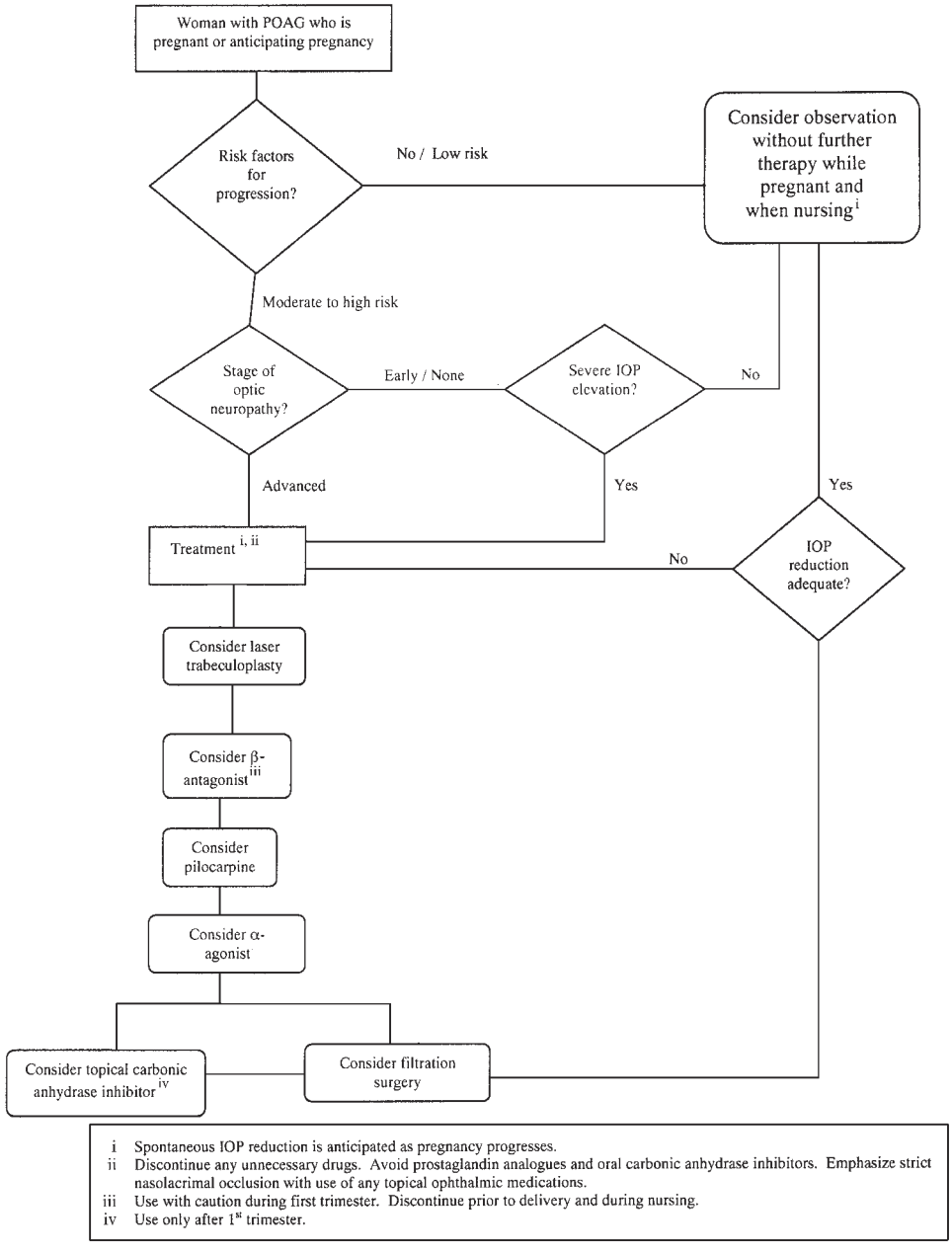

Figure 21–1. Suggested algorithm for management of POAG in pregnancy.

tinues to be challenging due to poorly defined risks. However, this uncommon clinical dilemma appears to attract little attention among glaucoma investigators, and it is anticipated that progress in this area will remain slow.

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◆ 22 ◆

Management of Blind, Painful Eye from Glaucoma

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Definition

How Is Blind, Painful Eye from Glaucoma Defined?

A blind, painful eye is defined as an eye that has no potential for any useful vision. The blindness is primarily due to glaucoma, although there could be associated ocular conditions, namely, retinal detachment, vascular occlusion, intraocular inflammation,[1] intraocular hemorrhage, previous ocular surgery, and tumors. Both primary and secondary forms of glaucoma may be encountered. The loss of vision is absolute, with minimal or no light perception, though certain patients have vision of hand movements. Other causes of pain are ruled out, such as corneal ulcers, corneal abrasions, scleritis, and infected scleral buckles.[2]

What Is the Etiology of Blind, Painful Eye from Glaucoma?

Almost all nerve terminals originating from the somatosensory receptors in the eye gather into the sensory root of the trigeminal nerve.[3] Both the short and long ciliary nerves arise from the nasociliary branch of the trigeminal nerve and supply the iris, sclera, trabecular area, ciliary body, and choroid. The iris is particularly densely supplied. The ciliary body also receives a plexus of fibers from the region of the scleral spur. Most of the sensory fibers are distributed in the anterior segment of the ciliary body.[3] Presumably, an elevated intraocular pressure (IOP) would affect these nerve endings, leading to significant ocular pain. The level of IOP does not always correspond with the degree of pain. The rate

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at which the IOP has increased plays a major role. A sudden sustained increase in IOP even to moderate levels may cause significant intraocular pain.[4] On the other hand, marked elevation in the IOP may not be associated with significant pain, if the pressure increase has been gradual. Presumably, the eye adjusts itself to the situation and remains comfortable.[4] The pain due to the rapid and persistent rise in IOP is described as a severe ache in the eye or the brow, or only as a severe headache.

A second cause of pain may be from varying degrees of intraocular inflammation, which may be secondary to intraocular vascular engorgement, with associated leakage of proteins and cells. The inflammation in the iris and the accompanying ciliary body spasm lead to pain that is referred and seems to radiate over a larger area served by the trigeminal nerve.[5] Intraocular inflammation usually accompanies secondary glaucomas, following vascular occlusion, retinal detachment, and uveitis. The degree of ciliary spasm does not necessarily correlate with the degree of intraocular inflammation, and younger patients tend to have more severe ciliary body spasm than older ones. A third cause of pain in blind glaucomatous eyes may be secondary to the surface abnormalities that may accompany such disorders. The most common are microcystic edema, bullae formation, and epithelial erosions secondary to corneal decompensation from increased IOP. Lastly, some patients may complain of pain after dellen formation, which may occur close to high filtering blebs or other lesions that may interfere with tear dynamics.

Epidemiology and Importance

How Common Is Blind, Painful Eye from Glaucoma?

Glaucoma is a significant cause of blindness in both the developing and the developed worlds.[6,7] It accounts for 7.5% of blindness in countries with established market economies, 8% in Latin America and the Caribbean, 12% in Africa and India, and up to 22.7% in China.[8] Studies by the World Health Organization suggest that the problem is greater than previously thought.[8] Most likely, glaucomatous blindness will continue to increase globally, reflecting aging populations and lack of sufficient eye care resources in poor countries.[8] Glaucoma was implicated in 6% of bilateral blindness in one study from Stockholm, Sweden. There are no available data on the incidence of unilateral blindness from glaucoma, though it may be significantly more than the above numbers suggest.

Are There Any Risk Factors Associated with Blind, Painful Eye from Glaucoma?

The risk factors are similar to those implicated in severe glaucoma. Generally, blindness from glaucoma in the elderly tends to be associated with primary open-angle glaucoma (POAG) and associated complications.[9] In this age group, blindness is slowly progressive, and usually painless. Conversely, blindness in younger patients results from acute secondary glaucoma, and is associated with a higher degree of inflammation. It is well recognized that blacks and Hispanics tend to develop a more severe form of glaucoma at a younger age.[10–12]

Secondary glaucomas may be at a higher risk of producing pain, because of the tendency to cause a more rapid increase in IOP than POAG. Closed-angle glaucoma and chronic angle-closure glaucoma can induce blindness, which may also be associated with significant intraocular pain.

Diagnosis and Differential Diagnosis

How Is Blind, Painful Eye from Glaucoma Diagnosed?

The degree of visual loss is severe and irreversible. The ocular examination should include visual acuity, which is usually light perception or no light perception (Fig. 22–1). IOP is usually high, although moderate IOPs could be associated with significant pain. Slit-lamp examination may show conjunctival hyperemia, corneal surface irregularities, corneal bullae, stromal edema, corneal opacification, corneal thinning, and keratic precipitates. The anterior chamber could be normal in depth. It can also be shallow, secondary to peripheral anterior synechiae, pupillary block, posterior synechiae with iris bombé, large lens, and intraocular tumors. The iris may be normal in appearance; however, iris atrophy, neovascularization, and vascular engorgement may be present. The pupil could be fixed and nonreactive to light stimulation. Such eyes may be phakic with normal lenses, but cataract is very common. Pseudophakia is also not uncommon. The vitreous may be hemorrhagic, or it could contain cellular inflammatory debris and membrane formation. A retinal detachment may be present. If the fundus cannot be visualized, then a B-scan echography should be performed to rule out intraocular tumors.[13–16] The tumors in such eyes are usually not detected early and tend to grow to significant size, and hence are more likely to produce pain, either secondary to the inflammation, or elevated IOP. Treatable causes of intraocular inflammation should be ruled out, such as sarcoidosis, sympathetic ophthalmia, human leukocyte antigen (HLA)-related uveitis, and autoimmune diseases. Also, exclude other causes of ocular pain, such as scleritis, corneal ulcers, infected scleral buckles, and orbital inflammatory diseases.

Treatment and Management

How Is Blind, Painful Eye from Glaucoma Managed?

The treatment of a blind eye secondary to glaucoma depends on the degree of blindness and pain. This chapter focuses on those eyes with no useful vision and that are painful (Fig. 22–1). Some of these eyes may have undergone one or more surgical procedures, some of which could be for the control of glaucoma. Others may have had no previous surgical intervention. A significant number of eyes, blind from glaucoma, are cosmetically acceptable, while some may be phthisical, irritable, and cosmetically unacceptable. Treatment of blind glaucomatous eyes should be directed toward the comfort of the patient and cosmetic appearance. It should not be directed toward a specific IOP reading. In fact, some patients may have a very high IOP, but with a normal-appearing, comfortable eye. Others may have lower IOP with significant irritation, pain, and poor cosmesis. The treatment is oriented toward three distinctively different groups.

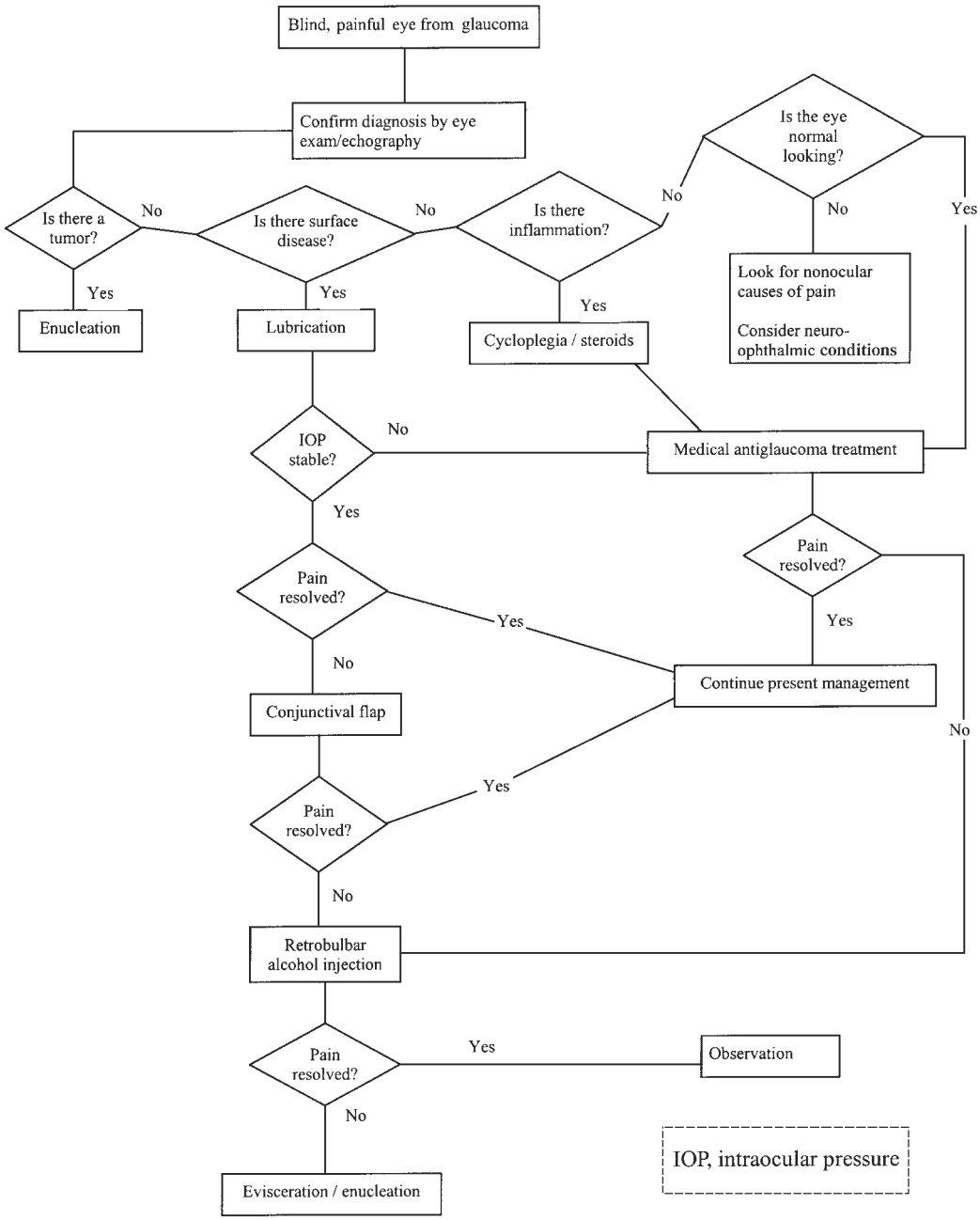

Figure 22–1. Management of a patient with blind, painful eye from glaucoma.

The first group has a normal-appearing globe with or without redness. This group can sometimes be satisfactorily treated by lowering the IOP by a few millimeters of mercury. One should avoid long-term carbonic anhydrase inhibitors, because of the systemic side effects.[17–19] It may also be wise to avoid using more than two or three topical medications because of side effects, cost,

and noncompliance. If the pain and the irritation are not controlled, an alternative treatment should be considered. One should also avoid the use of habit-forming analgesics.

The second group of glaucomatous blind eyes is characterized by intraocular inflammation, which may be secondary to extensive rubeosis irides, resulting from a variety of causes, such as vascular occlusions, previous surgeries, and tumors. This group can be treated with cycloplegic agents, typically atropine, and antiinflammatory agents, such as steroids or nonsteroidal antiinflammatory drugs. The cycloplegics help decrease the pain associated with ciliary spasm. The steroids help control the inflammation. Care should be taken to watch for secondary bacterial, fungal, and viral infections, especially herpes simplex outbreaks. One or two topical glaucoma medications may also be used. Cholinergic agents such as pilocarpine should be avoided because of their effect on the blood–aqueous barrier and ciliary spasm. The prostaglandin analogue latanoprost (Xalatan) may also increase intraocular inflammation.[20,21]

The third group of glaucomatous blind eyes is characterized by surface irritation, whether due to bullous corneal disease or calcification. These patients may present as an isolated entity or be part of the above-mentioned two groups.

When managing patients with blind, painful eyes, one should always keep in mind the patient as a whole. The majority of such patients are distressed, uncomfortable, and lead miserable lives. The preoccupation with their eyes overshadows other aspects of their lives and could lead to severe personal, emotional, and economic problems. If the pain is severe, they may not be able to carry on normal lives, and may thus lose their jobs. Another factor to consider is the increased frequency of their office visits. Because of the blindness, these patients do not drive, and hence depend on other family members for transportation. Thus, these visits are inconvenient; they are also costly. It is prudent to discuss these problems with the patient and family. Various treatment modalities and their risks and benefits should be mentioned. Management should be directed toward as quick a recovery as possible.

What Is the Medical Treatment?

Medical treatment should be safe, simple, and effective. If the pain is secondary to high IOP, a mild to moderate decrease in the pressure may resolve the pain. The objective here is not to maximally decrease the IOP, but to reduce it to an acceptable level. Such a decrease in IOP may be achieved by one or two topical medications, preferably with once or twice daily doses. If possible, one should avoid topical medications that require frequent instillation. Similarly, long-term use of systemic medications should be discouraged. Systemic carbonic anhydrase inhibitors tend to have more side effects and should not be part of a long-term treatment. Typically, a beta-blocker, prostaglandin analogue, α-$_2$ adrenergic agonist, or topical carbonic anhydrase inhibitors is the preferred medication. If the pain is secondary to intraocular inflammation, then a cycloplegic agent, preferably atropine, is necessary to control the ciliary body spasm, and obtain relief from pain. Topical steroids are used to control the inflammation. Patients should be informed of the potential of secondary bacterial, fungal, and viral infections. Systemic steroids should be avoided. If the

pain is secondary to a surface disease, then frequent corneal lubrication should be the treatment of choice. If a band keratopathy is present, one may consider chelation, although more aggressive surgical treatment may be appropriate.

Does Cyclocryotherapy Work?

Freezing of the ciliary body as a treatment of increased IOP has been well studied and extensively reported in the literature.[22–23] It can be used in refractory cases. The preferred approach is to treat 180 degrees of the ciliary body at a time. Most surgeons prefer a double freeze-thaw technique. The usual parameters are −80°C for 1 minute. The treatment consists of applying the cryoprobe 2 to 3 mm posterior to the limbus so as to create an iceball that just overlies the limbus. The aim is to cause the least amount of damage to functional trabecular meshwork. It is important to avoid the 3 and 9 o'clock positions, so that the two long posterior ciliary arteries are not damaged. About four or five partially overlapping cryoburns are usually sufficient. Cyclocryotherapy is highly efficacious and may be repeated if the result is unsatisfactory. Complications include persistent hypotony with extensive atrophy of the ciliary body, and the eye may end up as phthisis bulbi. Cyclocryotherapy may also prolong or induce intraocular inflammation. There have been a few cases reported in the literature of sympathetic ophthalmia, which could be devastating to the fellow eye, and hence, the patient should be warned of this potential complication.[24,25]

Does Laser Cyclodestruction Work?

Neodymium:yttrium-alumninum-garnet (Nd:YAG) laser has been reported as a treatment of high IOP, both in seeing and nonseeing eyes.[26–28] Al-Ghamdi et al[29] treated 47 patients with Nd:YAG laser, with the mean IOP dropping from 40.5 to 15.6 mm Hg. The treatment was performed after retrobulbar anesthesia, by applying laser burns 2 to 3 mm posterior to the limbus. A mean of 28 burns were applied with an average energy of 6 joules. Complications included intraocular inflammation, hypopyon, hyphema, hypotony, choroidal detachment, and flat anterior chamber.

When Should Retrobulbar Neurolytic Agents Be Used?

For a long time retrobulbar alcohol injection was the treatment of choice in blind painful eyes because of the simplicity of its delivery and apparent effectiveness.[30] Over the years, more and more potential severe complications were described, which made the procedure less popular. Complications include ptosis and external ophthalmoplegia. Recurrence of the pain is very common, necessitating repeated alcohol injections. Its effect on the orbital tissues is also of concern. Newer neurolytic agents commonly used in pain management have not been tried in the retrobulbar area.

What Is the Surgical Treatment of Blind, Painful Eye from Glaucoma?

In the absence of visual potential, intraocular glaucoma surgery is contraindicated, because of the risk of sympathetic ophthalmia.[31] It should also be

avoided because of postoperative complications, and the requirement for intensive follow-up care and a vigorous medication schedule. Any other planned surgical treatment must result in complete cessation of pain and provide good cosmesis. Most patients by this stage have had a long-standing loss of vision and significant pain or poor cosmesis. They usually request that their eye be removed. They have to be educated about the different procedures available. It should also be stressed that once such procedures are performed, there is complete irreversible loss, not only of vision, but also of the eye. However, they should be comforted about the effectiveness of this treatment. The patient and family need to be assured that such a procedure should control the pain and result in good cosmesis. Showing pictures of patients with prosthetic eyes is highly effective in decreasing the anxiety of patients regarding the postoperative cosmesis. Following removal of an eye, patients undergo a grief reaction with the characteristic denial followed by depression or anger and then acceptance and rehabilitation.[31]

What Is Evisceration?

Evisceration is a surgical procedure in which the intraocular contents are evacuated after the corneal tissue has been removed. The extraocular muscles are not disturbed, and the patient's own sclera acts as the wrapping around the orbital implant.[32,33]

What Is Enucleation?

Enucleation is a surgical procedure in which the eye is removed in total and intact. That includes the cornea, the sclera, and the intraocular contents. The extraocular muscles are preserved and some are attached to the orbital implant.[32,34]

What Are the Advantages and Disadvantages of Evisceration and Enucleation in the Management of Blind, Painful Eye from Glaucoma?

The literature is rich with cases of sympathetic ophthalmia following evisceration.[35,36] Because of this risk, the procedure of choice for a long time has been enucleation.[37] Reports in the literature dispute any significant risk of sympathetic ophthalmia.[38–40] Many surgeons perform evisceration if an intraocular tumor can be ruled out. Evisceration has some advantages over enucleation, namely limited changes in orbital anatomy and physiology.[32,33] Enucleations induce multiple changes in orbital anatomy and physiology, such as fat atrophy, decreased orbital soft tissue volume, changes in the levator muscle, and decreased orbital blood flow.[32] Eviscerations tend to have a better motility because the extraocular muscles are not disturbed. In enucleations, most surgeons would not reattach the oblique muscles, which leads to lesser motility as compared to eviscerations. Eviscerations are technically easier and are usually simpler and faster to perform. Compared to enucleations, there is limited perioperative morbidity and immediate and late operative complications. Enucleations, on the other hand, essentially eliminate the risk of sympathetic

ophthalmia and are safer in cases of occult or missed intraocular tumors. They also provide better specimens for pathologic examination, which in some cases may reveal important information concerning the pathogenesis of the visual loss in a variety of ocular disorders. Both procedures are generally performed under general anesthesia, but both could be performed under retrobulbar anesthesia, although it is more challenging with enucleations.

What Is the Surgical Technique in Evisceration?

After retrobulbar or general anesthesia, a 360-degree peritomy is performed and dissection in the sub-Tenon's space is carried out for 3 to 4 mm posterior to the limbus. With a no. 11 blade, a stab incision just posterior to the limbus is made. The cornea with a small rim of sclera is then resected with scissors. An evisceration spoon is then introduced between the uveal tissue and the sclera, and pushed gently posteriorly in the suprachoroidal space. Blunt dissection with the spoon is then carried over 360 degrees, releasing any adhesions between the choroid and the sclera. At this point, the intraocular contents usually present as an intact mass and are carefully evacuated. The specimen is then sent for pathologic examination. Any bleeding can be controlled with simple pressure. The inside of the sclera is then inspected for any residual uveal tissue. It is advisable to strip any remaining uvea from the sclera to minimize any stimulus for sympathetic ophthalmia. Once the sclera is void of uveal tissues, many surgeons introduce cotton wedges soaked with absolute alcohol and gently but thoroughly scrub the inside of the sclera. This may further decrease the possibility of sympathetic ophthalmia, by destroying any uveal tissues that may still remain in the scleral emissura. Care should be taken to prevent any contact of the alcohol with the conjunctiva because of the possibility of significant postoperative chemosis.

An appropriately sized sphere can then be inserted into the scleral pouch and the sclera sutured with multiple interrupted permanent sutures. The size of such a sphere in eviscerations is usually smaller than desired for optimal orbital volume replacement, hence necessitating a larger prosthesis. To be able to put a larger orbital implant, relaxing incisions in the sclera can be made in a vertical fashion starting from anterior to the equator and going all the way posteriorly to just before the optic nerve area.[33,35] A circular incision around the optic nerve can be made connecting these vertical incisions. This will cause the scleral pouch to significantly enlarge. A spherical implant of a larger size can then be inserted. Newer implants, such hydroxyapatite or Medpor, have the advantage of allowing vascularization. Hence, they become a living part of the orbit and decrease the potential long-term complications, especially migration of the implant. Tenon's capsule is then sutured with multiple interrupted 5-0 polypropylene sutures and the conjunctiva closed with a running 6-0 polypropylene suture. A conformer is then placed and a pressure dressing applied. The dressing should not be disturbed for 48 hours. Five weeks following evisceration, a prosthesis may be fitted.

What Is the Surgical Technique for Enucleation?

Enucleations are usually performed under general anesthesia, although retrobulbar anesthesia can be tried in certain patients.[41] After a 360-degree

peritomy, dissection is carried out in all of the four cardinal quadrants.[42–44] Each rectus muscle is then carefully isolated and disinserted from the globe, after securing a 5-0 polypropylene suture close to the insertion. The superior oblique muscle can be identified and cut. Similarly, the inferior oblique muscle can be isolated, cut, and cauterized. The stump of medial rectus muscle is then secured with a clamp, and the enucleation scissors introduced medial to the globe, directing posteriorly between the medial rectus muscle and the sclera, until the optic nerve is felt and engaged. The tips of the scissors should be directed posteriorly, and while applying pressure anteriorly on the medial rectus stump, the optic nerve is excised. This usually causes immediate protrusion of the globe. Any remaining adhesions between the globe and the orbital tissues are then carefully dissected. Immediate pressure is then applied to the orbit, using a sterile test tube wrapped in gauze. The risk of bleeding can be significantly decreased by first clamping the optic nerve before it is cut. In most cases, bleeding is controlled using a combination of pressure, cautery, and Gelfoam soaked with thrombin. An orbital implant, wrapped in donor sclera, is then introduced into the orbit, and each of the four rectus muscles is sutured to the sclera corresponding to its anatomic position. The rectus muscles can also be sutured directly to the orbital implant without a sclera wrap. A hydroxyapatite or a Medpor implant is preferred because of their ability to promote vascularization and thus decreasing the risk of migration. Tenon's capsule and conjunctiva are then closed in a manner similar to eviscerations. Similarly, a conformer and a pressure dressing are applied.

What Are the Complications of Evisceration and Enucleation?

The most dreaded intraoperative complication is removal of the wrong eye. This can be prevented by identifying and marking the eye to be operated on preoperatively. The mark should be applied above the correct eye and should be visible in the operative field. Hemorrhage is more common following enucleations, and may be profuse. It is best controlled by applying gauze packing and careful firm pressure following the removal of the globe. Cauterization and thrombin application may also be used appropriately. Injury to the medial orbital wall may be prevented by introducing the enucleation scissors medial to the globe rather than temporal. Similarly, perforation of the globe may be avoided by directing the enucleation scissors posteriorly into the orbit and applying anterior pressure on the media rectus stump. If perforation does occur, every attempt should be made to identify the remaining part of the globe and resecting meticulously. Postoperatively, complications include wound dehiscence with extrusion of the orbital implant. This can be avoided by careful closure of the Tenon's capsule and conjunctiva in separate layers. Implant migration may be minimized by using hydroxyapatite or Medpor implants. Other complications include ptosis, enophthalmos, shallowing of the fornices, superior sulcus deformity, and orbital cysts.[45]

What Are the Considerations in Children?

The growth of the orbit in children is dependent on the presence of an enlarging globe. A marked increase in the size of the globe from congenital glaucoma

leads to a larger bony orbit, and hence facial asymmetry in children. An absence of a globe will remove the stimulus for a normal enlargement of the bony orbit and hence asymmetry in unilateral cases. Normally, the bony orbit achieves almost adult size by the age of 3 years. Children who undergo enucleations or eviscerations should be followed closely by an ophthalmologist and an oculist, especially those younger than 3 years of age, to ensure adequate development of the bony orbit. This could be achieved by progressively increasing the size of the prosthesis and in some cases larger orbital implants may be needed.

Future Considerations

With the improvement in pain management, newer agents may contribute to better control of pain without the need for removal of the eye.

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