

Open-angle glaucoma: Tips for earlier detection and treatment selection

Ahmad A. Aref, BS

Feinberg School of Medicine, Northwestern University, Chicago, Ill

Brian P. Schmitt, MD, MPH, FACP

Feinberg School of Medicine, Northwestern University and the VA Chicago Health Care System

Practice recommendations

- Screen persons older than 60 years, African Americans of any age, and those with a family history of open-angle glaucoma (**C**). Further evaluation by an ophthalmologist is warranted if optic nerve damage is suspected or if a patient reports decreasing vision.
- Elevated intraocular pressure (IOP) is not necessary for open-angle glaucoma to occur. Assess optic nerve status and visual field in those at risk. (**C**)
- Inquire about topical ocular drops recommended by an ophthalmologist, to be certain they are not contraindicated for other conditions the patient might have, and to be alert to the potential for adverse effects. (**C**)

Evaluate for open-angle glaucoma (OAG) when a patient reports decreased vision, or when a patient even with good eyesight is found to be at high risk for the disease. Most

Corresponding author: Ahmad A. Aref, BS, 401 East Ontario St, Suite 710, Chicago, IL 60611. E-mail: a-aref@md.northwestern.edu.

patients with early glaucoma are unaware of the initial decrease in peripheral vision.¹

A relatively new diagnostic technique can detect even moderate damage to the optic nerve, and the procedure is brief. Ophthalmologists can choose from among several topical medications to reduce intraocular pressure. Your knowledge of the patient's medical history is critical to avoiding potential drug-drug interactions.

Laser surgery and trabeculectomy may be indicated as first-line therapy for select patients.

■ WHOM TO SCREEN

Persons aged older than 60 years, African Americans of any age, and those with a family history of OAG are at particularly high risk, and all risk factors should be fully assessed (SOR: **B**).² (See **Open-angle glaucoma: The scope of the problem.**)

In the Caucasian population aged 40 to 49 years with no family history of OAG, disease prevalence is just 0.18%. Prevalence is 4 times greater in African Americans of the same age range. Caucasians aged 60 to 69 years have a prevalence of OAG 4 times greater than patients aged 40 to 49. For African Americans older than 80 years, prevalence exceeds 11%.³

For persons with a first-degree relative with OAG, risk was found to be 9.2 times greater than for those without such a history.⁸

Open-angle glaucoma: The scope of the problem

Open-angle glaucoma (OAG) is defined as an optic neuropathy in which there is damage to the optic nerve with a loss of retinal ganglion cells that carry visual impulses from the eye to the brain. It is the second most common cause of legal blindness in the United States and the leading cause of blindness among African Americans.² A population-based evaluation of glaucoma screening, the Baltimore Eye Survey, estimates about 2.5 million Americans as having OAG with as many as half of them unaware that they have the disease.^{3,4}

More than 8 million office visits to office-based clinicians occur per year by patients with a primary diagnosis of glaucoma.⁵ The National Eye Institute, a division of the NIH, reports that as many as 120,000 Americans are currently blind as a result of glaucoma, costing the US government over \$1.5 billion annually in Social Security benefits, lost income tax revenues, and health care expenditures.

An asymptomatic disease in its early stages,¹ glaucoma progresses to cause permanent blindness in the absence of treatment. This article addresses the features, diagnostic methods, and treatment modalities of glaucoma as well as the role of the family physician in its management.

What causes OAG?

The pathogenesis of glaucoma is multifactorial and is thought, in most cases, to be caused by an abnormally high intraocular pressure (IOP), which mechanically compresses and causes subsequent atrophy of optic nerve fibers. The increased pressure is due to impaired drainage of aqueous humor out of the eye. Aqueous humor, produced by the ciliary body, normally provides nutrients to the iris, lens, and cornea before being drained through the trabecular meshwork.

It should be noted, however, that an elevated IOP is not necessary in glaucoma; optic nerve atrophy can occur in the absence of high IOP. The mechanism for optic nerve damage in this form of glaucoma is unknown.⁶

In angle-closure glaucoma, the angle between the iris and the trabecular meshwork is occluded, preventing normal drainage of aqueous humor. In open-angle glaucoma, the angle appears open but does not function properly in draining aqueous humor out of the eye.⁶ It is open-angle glaucoma that will be discussed here as it accounts for 75% to 95% of all glaucoma cases.⁷

Ask specifically about decreased vision, loss of peripheral vision, difficulty seeing in the dark, and difficulty reading (SOR: **B**).

Before referring high-risk patients for a full ophthalmologic examination, examine the optic nerve with direct ophthalmoscopy (SOR: **B**).

Determining optic nerve status

Examination of the optic nerve head provides clues as to whether structural damage has occurred. Cup-disc ratio is used to assess risk of glaucoma development. The probability of abnormality increases dramatically for values above 0.5.⁹

The standard clinical technique used by primary care clinicians is with the direct ophthalmoscope. Sensitivity and specificity for a cup-disc ratio greater than 0.6 have been reported to be 64% and 96%, respectively, using direct ophthalmoscopy.¹⁰

Ophthalmologists use stereoscopic fundus photography to visualize the optic nerve. With this technique, sensitivity and specificity for a cup-disc ratio greater than 0.5 have been found to be 48% and 89%, respectively.¹¹ Studies, however, have reported a high interobserver variation in measurement of the cup-disc ratio even among experts in the field.¹²

TABLE 1

Characteristics of diagnostic tests for open-angle glaucoma

Test	Study quality	Sn%	Sp%	LR+	LR–	PV+	PV–
Tonometry ¹⁴ IOP >21 mm Hg IOP <21 mm Hg	2	47.1	92.4	6.20	.57	24.6	97
Cup-disc ratio, stereoscopic photography ¹⁴ Cup-disc ratio >.5 Cup-disc ratio <.5	2	48	89	4.36	.58	.187	97
Cup-disc ratio, direct ophthalmoscopy ¹⁰ Cup-disc ratio >.6 Cup-disc ratio <.6	1	64	96	16	.375	46	98
Visual field ¹⁵ Abnormal Normal	2	97	84	6.06	.036	24.2	99.8

LR+ = positive likelihood ratio; the likelihood that a person with OAG will have a positive test result (eg, a person with OAG is 16 times more likely to exhibit a cup-disc ratio >.6 than a person without the disease). **See “Using the likelihood ratio,” page 127 of this issue.**

LR– = negative likelihood ratio; the likelihood that a person with OAG will have a negative test result (eg, a person with OAG is only .375 times as likely to exhibit a cup-disc ratio <.6 as a person without the disease)

PV+ = positive predictive value; the probability that a positive test result indicates disease

PV– = negative predictive value; the probability that a negative test result indicates absence of disease

PV+ and PV– assume a baseline likelihood of disease of 5% (prevalence among African Americans aged 60–69 years)³

What to look for. Characteristic changes include narrowing or notching of the neuroretinal rim, or characteristic visual field loss, such as arcuate defects and nasal loss.¹³ Describe an abnormal optic disc in terms of its cup-disc ratio, and report visual loss to the ophthalmologist as a defect in a respective field quadrant as detected on confrontational visual field testing or as an afferent pupillary defect in a given eye.

Referral. A final diagnosis of open-angle glaucoma can be made only after characteristic damage to the optic nerve has been confirmed by an ophthalmologist (SOR: **B**). Therefore, patients at high risk of developing OAG (age >60 years, African American race, positive family history) should be referred for an eye examination.

Other key diagnostic tests include measurement of intraocular pressure and visual field testing.² The accuracy of these tests is outlined in **Table 1**.

Intraocular pressure: Caveats

Intraocular pressure (IOP) is measured by a tonometer. The eye is subjected to a force that flattens the cornea. This force is then related to the pressure in the eye, or IOP. The standard instrument for measuring IOP is the Goldman applanation tonometer. Handheld versions (tonopen) are useful for screening by the primary care clinician.¹¹ Studies of IOP distribution show the normal range of IOP values to be less than 21 mm Hg with a slight skew towards higher values.¹⁶

The altering effect of corneal thickness. IOP measurement may vary with the thickness of one's cornea. A corneal thickness greater than 555 μ m can produce falsely high readings, and a corneal thickness less than 540 μ m can produce falsely low readings.^{2,17,18} Thus, central corneal thickness (CCT) is a factor that may affect the accuracy of an IOP reading. Central corneal

thickness is measured with a pachymeter, and an ophthalmologist must take this measurement into account when assessing a patient's IOP.

Pressure may not be elevated in OAG. A number of population-based studies have documented an increase in the prevalence of OAG with an increase in IOP.^{7,19,20} However, these same studies have also concluded that many patients with OAG have IOP levels in the normal range. These patients are deemed to have normal pressure glaucoma (NPG), a subtype of OAG.²¹

Likewise, many patients with elevated IOP have no demonstrable optic nerve damage;^{19,20} this condition has been termed ocular hypertension (OHT).

A proper perspective. So, although an elevated IOP is associated with glaucoma, it is important to note that OAG is not defined by the presence of an elevated IOP. Optic nerve atrophy can occur in the absence of an increased IOP.²¹ These findings, taken together with the variance of IOP with CCT, are reflected in the modest sensitivity and specificity for IOP readings greater than 21 mm Hg—47.1% and 92.4%, respectively.¹⁴ Patients with a high IOP (>21 mm Hg) are at higher risk for developing OAG, but further ancillary studies and tests are necessary to confirm the diagnosis.¹³

Evaluating the visual field

Visual field deterioration is the final manifestation of glaucoma. Vision is first lost peripherally. Central vision loss occurs at the end stage of the disease.

An ophthalmologist will use automated static threshold perimetry to evaluate the visual field. With this technique, the patient must identify white target lights of variable brightness in different locations of a dim 1-m bowl. Various data algorithms are then employed to compare any abnormality in the visual field with patterns that are characteristic of glaucoma.⁹ One study reported a 97% sensitivity and 84% specificity using a certain algorithm to recognize field abnormalities due to glaucoma.¹⁵ However, auto-

mated perimetry requires 10 to 20 minutes per eye, and patient fatigue often reduces reliability of the test. Also, an optic nerve head has typically undergone considerable damage before visual field changes are detected.²

An improved test. Frequency doubling technology promises to detect glaucomatous visual defects when there has been only moderate damage to the optic nerve. With frequency doubling technology, patients must recognize patterns of alternating light and dark bars. An abnormality in recognition is thought to be indicative of the pattern of field loss in glaucoma. One study found a sensitivity and specificity each greater than 90% for identifying patients thought to have glaucoma. Another benefit is that the exam takes an average of only 6 minutes to complete in both eyes.²²

No single test result is enough

Successful screening for glaucoma should not rely solely on measuring IOP, assessment of the optic nerve, or visual field testing. These diagnostic clues are complementary and must be taken together to evaluate high-risk populations, including African Americans, those with a family history of glaucoma, and the elderly (SOR: C).

■ REGULAR FOLLOW-UP

Regardless of findings, patients aged 40 to 60 years should be encouraged to have eye exams every other year, and those over age 60 should have annual eye exams (SOR: B).¹³ Regular ocular exams including vision check, extraocular muscle exam, papillary exam, and confrontational visual fields should be performed in these patients as well (SOR: C).

■ TREATMENT

IOP is the only risk factor for glaucoma that can be treated. Lowering IOP in randomized control trials has reduced the progression of visual field loss in OAG patients with abnormally high pressures²³ as well as in NPG patients with pressures in the normal range.²⁴

TABLE 2

Pharmacologic options for patients with open-angle glaucoma

Medication (SOR)	% IOP reduction	% RR*	NNT to prevent visual field loss*	Side effects	Comments
Beta-blockers (A), <i>non-selective</i> (timolol, carteolol, levobunolol, metipranolol) and <i>selective</i> (betaxolol)	31	74	2.17	Bradycardia, hypotension, bronchospasm (timolol, carteolol, levobunolol, metipranolol)	Cochrane review with clear recommendation as first-line treatment ²¹
Prostaglandin analogues (A) (latanoprost, travoprost, unoprostone)	40	96	1.68	Increased eyelash growth, iris pigmentation, muscle and joint pain	Multiple RCTs and systematic review show clinical and statistical superiority over beta-blockers ^{26,27}
Alpha adrenergic drugs (A) (apraclonidine, brimonidine)	23	55	2.93	Dry nose, dry mouth, follicular conjunctivitis, hypotension (brimonidine)	Multiple RCTs support effectiveness ²⁸⁻³⁰
Topical carbonic anhydrase inhibitors (A) (brinzolamide, dorzolamide)	26	62	2.6	GI disturbances, headache, local irritation, redness, sulfa allergies	RCT, ³¹ Cochrane review with clear recommendation ²⁶
Cholinergic agonists (A) (pilocarpine, carbachol)	29	69	2.32	Small, fixed pupils, induced myopia, cataracts	Consistently recommended as second- or third-line drugs in systematic reviews and RCTs ^{27,32}

*Percent decrease in risk of visual field loss and NNT to prevent visual field loss were calculated for a patient with a baseline IOP of 24 mm Hg.

SOR, strength of recommendation; IOP, intraocular pressure; RR, relative risk; NNT, number needed to treat; RCT, randomized controlled trial.

In the Early Manifest Glaucoma Trial, a 30% reduction in IOP reduced the rate of progression in the treatment group (45%) compared with the control group (62%; $P=.007$).²⁵ Progression risk decreased by approximately 10% per mm Hg of IOP reduction.

Setting a target pressure. Before beginning therapy, an ophthalmologist sets a target pressure that should halt further optic nerve damage. The initial target pressure is usually 20% to 30%

lower than the pretreatment pressure. If damage to the optic nerve is already substantial, the target pressure may be set even lower.²

Stepwise therapy. Topical medications are usually given first, as eye drops. A comparison of these medications is outlined in **Table 2**. If IOP cannot be lowered pharmacologically, argon laser trabeculoplasty (ALT) is the next step. If the pressure still cannot be lowered, filtering surgery is the final alternative (SOR: C).²

Make sure topical ocular drops are not contraindicated and be alert for potential adverse effects

Pharmacologic options

Medical agents work in 1 of 2 ways to lower IOP: by decreasing production of aqueous humor, or by increasing drainage of aqueous humor out of the eye. Though most glaucoma medications are given topically, severe systemic side effects can occur.² Because the consulting ophthalmologist may not be aware of a patient's other medical conditions, inquire about the topical ocular drops being recommended to make certain they are not contraindicated and to be alert to the potential for adverse effects (SOR: C).¹³

Beta-adrenergic antagonists can lower IOP by up to 31%²⁵ and are often used as first-line treatment (SOR: A).²¹ However, nonselective beta-blockers (timolol, carteolol, levobunolol, metipranolol) are associated with a number of adverse effects including bronchospasm,³³ bradycardia, and hypotension.³⁴

Betaxolol is a selective beta-blocker with less tendency to cause pulmonary side effects,³⁴ but it may still do so in patients with severe pulmonary disease.³⁵ Selective beta-blockers lower IOP to a lesser degree than nonselective drugs³⁶ and can cause the same cardiac effects of bradycardia and hypotension.³⁸

Prostaglandin analogs (latanoprost, travoprost, unoprostone) increase drainage of the aqueous humor. Prostaglandins are clinically and statistically superior to beta-blockers, having lowered IOP by up to 40% in randomized controlled trials.³⁷ Side effects include increased eyelash growth and iris pigmentation,²⁶ and muscle and joint pain.³⁸

Alpha-adrenergic drugs (apraclonidine, brimonidine) lower aqueous humor production. Apraclonidine administered topically does not cross the blood-brain barrier, effectively lowering IOP without causing cardiovascular side effects.²⁸ The most common side effects are dry nose, dry mouth,²⁸ and follicular conjunctivitis.²⁹ Unlike

apraclonidine, brimonidine crosses the blood-brain barrier and can cause mild hypotension.³⁰ One randomized controlled trial found no statistical difference in efficacy between brimonidine and apraclonidine, both lowering IOP by up to 23%.³⁹

Carbonic anhydrase inhibitors block water flow into the eye, preventing aqueous humor formation. Until recently, carbonic anhydrase inhibitors such as acetazolamide were administered only orally and adverse effects were therefore common.²⁷ Topical carbonic anhydrase inhibitors (brinzolamide, dorzolamide), recently introduced, lower IOP by up to 26% and with few side effects.³¹

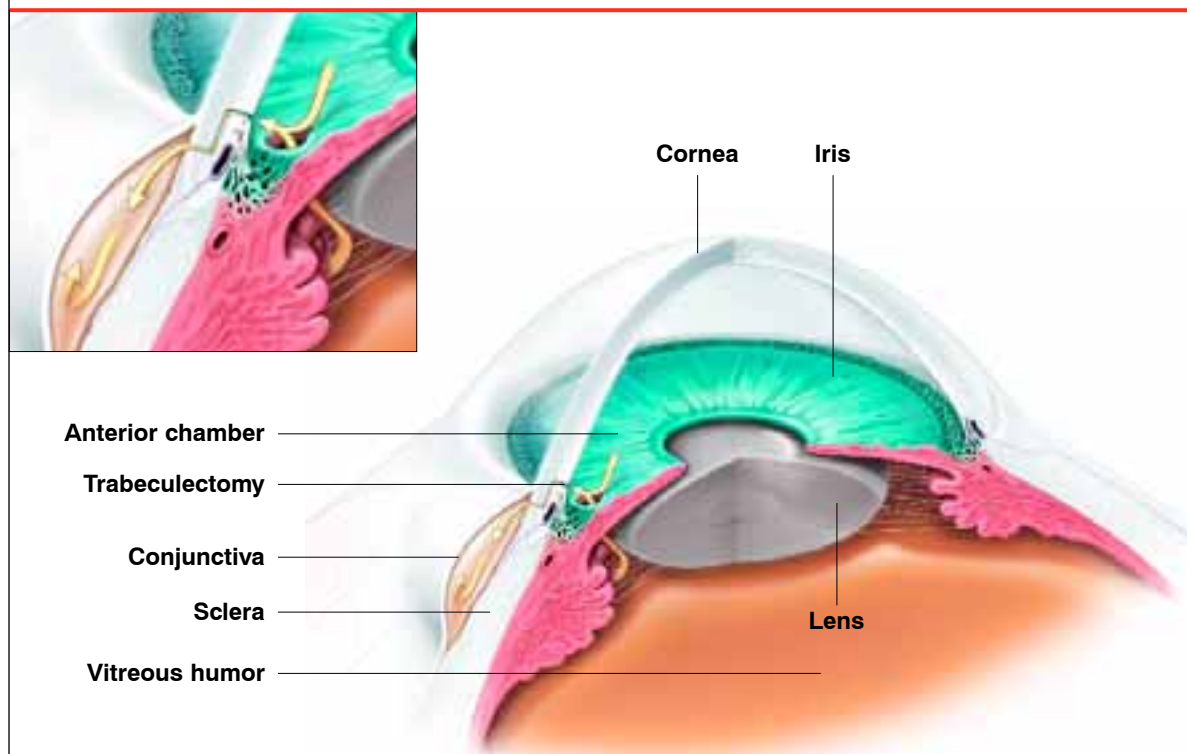
Cholinergic agonists (pilocarpine, carbachol) increase aqueous outflow from the eye by stimulating contraction of the ciliary body, which opens the trabecular meshwork to allow further drainage.⁴⁰ Because of its ocular side effects including small, fixed pupils, induced myopia, and cataracts, pilocarpine is reserved for second- or third-line therapy (SOR: A).^{9,27,32}

Medicinal marijuana used to lower IOP in glaucoma patients is controversial. The primary active ingredient in marijuana, tetrahydrocannabinol (THC), lowers IOP when inhaled. However, it lowers IOP for only 3 hours, and glaucoma management requires a constant reduction in IOP. Due to its intense side effects of altered mental status, tachycardia, and systemic hypotension, medicinal marijuana is not desirable for the treatment of glaucoma.⁴¹

Benefit in combining regimens. Using different classes of drugs produces an additive effect in lowering IOP, so the ophthalmologist may use up to 3 drugs simultaneously. When therapy is begun, a topical drug is often applied to only 1 eye, letting the opposite eye serve as a control. If IOP is not lowered in the treated eye when compared with the control eye, the drug is discontinued (SOR: A).²⁷

Dealing with noncompliance. More than one third of patients exhibit poor compliance with therapy,⁹ and strict adherence to the regimen is necessary to lower IOP. Instruct patients in proper techniques for taking and using medica-

FIGURE

Filtering surgery for glaucoma

Trabeculectomy or filtering surgery creates a passageway for aqueous fluid inside the eye to escape, thereby lowering pressure. The filter drains the fluid from the anterior chamber to an area that is created between the conjunctiva and the sclera. This fluid will eventually be absorbed by blood vessels.

ILLUSTRATION BY RICH LAROCCA

tions, and record dosage and frequency at each physician visit.

Advise patients that glaucoma can progress, but that blindness is not inevitable. Stress the importance of adhering to the prescribed treatment regimen (SOR: C).¹³ If poor compliance remains an issue, let the patient know that therapeutic alternatives may be possible (SOR: C).²

Argon laser trabeculoplasty

Argon laser trabeculoplasty (ALT) is an outpatient procedure. Laser energy is directed at the trabecular meshwork to facilitate aqueous humor outflow. In a large clinical trial with long-term follow-up, initial ALT therapy was found to be at least as

effective as initial pharmacological treatment.⁴²

Medical treatment is often continued after ALT.⁴³ In the Early Manifest Glaucoma Trial,²⁵ glaucoma patients randomized to receive ALT therapy plus a topical beta-blocker (betaxolol) had a 30% reduction in IOP. Compared with the control group, patients treated with ALT and beta-blocker exhibited half the risk of visual field deterioration, with a number needed to treat of 2.24 to prevent field loss in a patient with a baseline IOP of 24 mm Hg.

Surgery

Although surgical treatment is generally considered a final alternative in management, it may be

an appropriate first-line therapy for patients with cardiovascular or pulmonary conditions contraindicating use of medical therapy.¹³

Filtering surgery (trabeculectomy) (**Figure**) is an outpatient procedure wherein IOP is lowered by creating a fistula in the globe of the eye to drain aqueous humor into the sub-conjunctival space.²¹ In a randomized controlled trial, trabeculectomy used alone or with medical therapy in a previously unoperated eye successfully lowered IOP by a rate of 85% to 95% at 2 years.⁴⁴ At 5 years, the success rate in Caucasians is 90%; in African Americans, 80%.⁴⁴ However, a recent meta-analysis suggests that glaucoma surgery is associated with accelerated progression of cataract.⁴⁵ The Collaborative Initial Glaucoma Treatment Study (CIGTS) found 3 times the incidence of cataract surgery among subjects randomized to initial filtration surgery as opposed to medical management ($P=.0001$).⁴⁶

■ PROGNOSIS

Glaucoma progresses insidiously. Peripheral vision is lost first in early stages of the disease and may not even be noticed by the patient. Central vision is spared until late stages of the disease.

Blindness can usually be prevented if glaucoma is detected early and IOP is lowered sufficiently.⁴⁷ Unfortunately a small number of patients may suffer irreversible vision loss even with adequate treatment; they should be referred for low-vision rehabilitation and social services (SOR: C).² In May 2002, the Centers for Medicare and Medicaid Services approved Medicare coverage for these services.⁴⁸ Services offering rehabilitation for those with low-vision: Prevent Blindness America (preventblindness.org), National Federation of the Blind (www.nfb.org), National Library Service for the Blind and Physically Handicapped (www.loc.gov/nls), and the Foundation Fighting Blindness (www.blindness.org).

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DRUG BRAND NAMES

Amlodipine • Norvasc
 Acetazolamide • AK-Zol; Diamox
 Apraclonidine • Iopidine
 Betaxolol • Betoptic
 Brimonidine • Alphagan
 Brinzolamide • Azopt
 Carbachol • Carbastat, Carboptic, Isopto Carbachol, Miostat
 Carteolol • Ocupress
 Dorzolamide • Trusopt
 Latanoprost • Xalatan
 Levobunolol • AKBeta, Betagan
 Metipranolol • OptiPranolol
 Timolol • Timoptic
 Travoprost • Travatan
 Unoprostone • Rescula