34. Screening for Glaucoma

RECOMMENDATION

There is insufficient evidence to recommend for or against routine screening for intraocular hypertension or glaucoma by primary care clinicians. Recommendations to refer high-risk patients for evaluation by an eye specialist may be made on other grounds (see ***Clinical Intervention***).

Burden of Suffering

Glaucoma is a disorder defined by slowly progressive loss of vision in association with characteristic signs of damage to the optic nerve. Selective death of retinal ganglion cells leads to the gradual enlargement of the optic cup and loss of vision (beginning with peripheral vision) that are typical of glaucoma.[1] Increased intraocular pressure (IOP) is common in glaucoma and is believed to contribute to the damage to the optic nerve, but it is no longer considered a diagnostic criterion for glaucoma. Glaucoma is the second leading cause of irreversible blindness in the U.S., and the leading cause among African Americans.[2,3] Of the various forms of glaucoma (e.g., congenital, open-angle, closed-angle, secondary), primary open-angle glaucoma (POAG) is the most common in the U.S. (80–90% of cases)[4] and is estimated to be responsible for impaired vision in 1.6 million Americans and blindness in 150,000.[1,4] Annual office visits for glaucoma increased from roughly 2 million in 1975 to almost 9 million in 1992.[4a] POAG is usually asymptomatic until irreversible visual field loss has occurred. One study reported that over the course of 20 years, blindness may develop in up to 75% of persons with glaucoma.[5] There are few data, however, on the natural history of disease in persons with mild visual field defects detected by screening.

The prevalence of glaucoma is 4–6-fold higher in blacks than whites, and it increases steadily with age: among whites, glaucoma is present in 0.5–1.5% of persons under age 65 and 2–4% of those over 75;[6,7] among blacks, 1.2% of 40–49-year-olds and 11.3% of those over 80 have glaucoma.[8] Prevalence of glaucoma is increased in patients with diabetes mellitus, myopia, and a family history of glaucoma.[1] A much larger number of persons have ocular hypertension (usually defined as an IOP > 21 mm Hg), which is a strong risk factor for developing glaucoma. Ocular hypertension is present in 7–13% of the

general population, prevalence increasing with age.[3] In the Framingham Study, one fourth of men and women over age 65 had ocular hypertension.[9] The risk of progressing to glaucoma varies directly with level of IOP and duration of follow-up: the proportion of persons developing visual deficits within 5 years was less than 1% for normal IOP (<21 mm Hg), 3–10% for IOP ≥ 21 mm Hg, 6–16% for IOP > 25 mm Hg, and 33% for IOP > 30 mm Hg.[10] Untreated individuals with moderate ocular hypertension (mean IOP 24–26 mm Hg) developed new visual deficits (based on sensitive measures) at a rate of 3–4% per year in recent trials.[11–13] Among patients with untreated ocular hypertension followed for 17–20 years in older series, over 30% developed clinical glaucoma.[14,15]

Accuracy of Screening Tests

There are two potential targets for screening among asymptomatic persons: individuals who have normal vision but are at increased risk for developing glaucoma (i.e., "glaucoma suspects"), and those who have undetected visual field defects (i.e., undiagnosed glaucoma). Up to 50% of persons with glaucomatous visual deficits detected by screening are unaware of their diagnosis.[8]

The three most common screening tests for glaucoma are tonometry, ophthalmoscopy, and perimetry. Tonometers, which include Schiötz, applanation, and noncontact (air puff) devices, are used to measure intraocular pressure. The accuracy and reliability of tonometry is affected by the choice of device, the experience of the examiner, and physiologic variables in the patient.[10,16] The more fundamental problem with tonometry as a screening test is the limited sensitivity and specificity of elevated IOP for current or future cases of glaucoma. Many patients with ocular hypertension (perhaps more than 70%) will never develop vision problems due to glaucoma.[14,15] Isolated measurements of IOP are also insensitive for glaucoma: only half of all patients with documented glaucoma have IOP greater than 21 mm Hg on random measurement, due in part to fluctuations in IOP over time.[4,17] There is no single cutoff value of IOP that provides an acceptable balance of sensitivity and specificity for screening.[1] In the Baltimore Eye Survey, a cutoff of IOP > 18 mm Hg had a sensitivity and specificity of 65% for definite or probable glaucoma; raising the cutoff to 21 mm Hg improved specificity to 92%, but lowered sensitivity to 44%.[4] In population screening, where prevalence of glaucoma is relatively low, less than 5% of those with ocular hypertension will have documented glaucoma.[18]

A second screening test for POAG is direct ophthalmoscopy or slit-lamp examination, which can detect the changes in the optic nerve head (e.g., cupping, pallor, hemorrhage) that often precede the development of visual deficits in glaucoma. Examining the optic disk to screen for glau-

coma in the primary care setting is limited by considerable interobserver variation in interpretation of funduscopic findings, even among experts using standardized criteria.[19] Ophthalmologists using direct ophthalmoscopy alone detected fewer than one half of all cases of glaucoma.[20] Primary care clinicians with less skill in ophthalmoscopy and less time to dilate pupils would be expected to have poorer accuracy. Qualitative evaluation of stereoscopic photographs of the optic disk is more sensitive,[21] and disc photography allows for precise measures of disk parameters, which may provide evidence of glaucomatous nerve damage (e.g., vertical and horizontal cup-disk ratios, neuroretinal rim width). No combination of parameters, however, adequately discriminates patients with glaucoma from normal subjects. In the Baltimore survey, various combinations of disk parameters, IOP, and family history had only moderate sensitivity (49–66%) and specificity (79–87%) for glaucoma.[4] Neither slit-lamp examination nor optic disk photography is routinely available in the primary care setting.

The third method of screening for POAG is perimetry, in which patients respond to visual stimuli of varying brightness presented in various locations in their visual field. Reproducible visual field defects currently represent the "gold standard" for diagnosing glaucoma, but diagnostic testing with automated perimetry may take more than 45 minutes and is not feasible for screening.[1] Modified testing strategies can reduce the time needed for screening, but they are less sensitive and specific for glaucoma. Evaluations of these devices report a sensitivity in excess of 90% and a specificity of 70–88%.[17,22,23] False-positive results can be caused by visual disorders other than glaucoma and by unfamiliarity of patients with the testing process. Due to expense and technical difficulties, automated perimetry is not practical for routine use in the primary care setting. Moreover, visual field loss is often a late event in the natural history of glaucoma: by the time visual deficits are evident, up to 50% of nerve fibers may have been lost.[24] Newer techniques (e.g., computer-assisted imaging, specialized photographic methods) for assessing changes in the optic nerve may prove more sensitive for early injury, but they are currently too complicated or expensive to be used for routine screening.[1,17]

Effectiveness of Early Detection

Visual deficits due to glaucoma are not generally reversible, but early treatment is widely believed to prevent or delay the progression to more serious vision problems. The assumption that lowering intraocular pressure improves outcome in patients with glaucoma is based primarily on indirect evidence, however: the strong association between level of intraocular pressure and risk of POAG, the deleterious effects of raised IOP in secondary glaucoma and in animal models, and the progressive nature of un-

treated glaucoma. Controlled studies of treatment of glaucoma have generally compared different modes of therapy with each other, rather than comparing treatment to no treatment.[25] The majority of patients experience continuing loss of vision despite treatment, however, and change in IOP does not reliably distinguish patients who progress on treatment from those with stable disease.[26,27] A few observational studies have reported a higher incidence of disease progression in those receiving treatment than untreated patients, but these findings are probably biased by more severe disease in treated subjects.[10] Some indirect evidence of treatment effectiveness is provided by a report from Denmark of declining incidence of blindness due to glaucoma over the past 30 years.[28] The disparity in the rates of glaucoma and glaucoma blindness among white and black Americans may also reflect greater access to effective treatment among whites, although the higher prevalence of glaucoma among blacks may have a biologic basis as well.[2,29] Nonetheless, for many patients who would be detected by screening, especially those with mild visual field defects and moderate elevations of intraocular pressure, the natural history of disease and the benefits of early treatment remain uncertain. The Early Manifest Glaucoma Trial, currently under way in Sweden, is randomizing such patients to early treatment with medications and laser therapy or no initial treatment (M.C. Leske, personal communication, Stony Brook, NY, March 1995).

A larger number of controlled studies has been conducted among patients with elevated IOP but no visual deficits. Early trials suffered from various methodologic problems, including small size, insufficient follow-up, or use of less reliable methods for determining visual changes.[30–33] Three recent, well-designed studies have compared ocular timolol treatment to no treatment (or placebo) in patients with normal visual fields and moderate elevations of IOP (<35 mm Hg, mean 24–26 mm Hg). These studies each enrolled larger numbers of patients, followed subjects between 4–8 years, and used automated perimetry to detect or confirm new visual field deficits. A study by Kass et al. randomized one eye to active treatment (and one to placebo) in 62 patients. After 5 years of treatment, new visual deficits developed in 4 timolol-treated eyes and 10 placebo-treated eyes, a result of borderline statistical significance.[11] Systemic effects of timolol on placebo-treated eyes may have diminished the apparent benefit of treatment. A second study by Epstein et al. randomized 107 patients to timolol or placebo: 9 patients on placebo (vs. 4 on active treatment) developed new visual field defects. The benefits of treatment were of borderline significance ($p = 0.07$) using a combined endpoint of visual field changes, increase in cup-disk ratio, or progression to more severe intraocular hypertension (IOP > 32 mm Hg).[12] In contrast, Schulzer et al. found no benefit of timolol treatment, despite enrolling more subjects and more ef-

fectively lowering IOP than previous trials (mean 4.5 mm Hg).[13] Over a 6-year study, there were no differences between treated and untreated subjects in the progression to new visual field deficits, disk hemorrhage, or change in photographic appearance of the optic disk. Neither mean IOP nor change in IOP predicted progression of disease in subjects using timolol. The power of each of these trials was reduced by substantial dropout rates among treated subjects (up to 25%).

A meta-analysis of these three trials estimated that treatment reduces the proportion of patients who develop new visual deficits by 25%, but it could not rule out a possible harmful effect of treatment.[25] The difficulty in demonstrating a significant effect in previous clinical studies may be due in part to variations among individuals in their sensitivity to raised IOP, modest effects of treatment on IOP, and poor long-term compliance with therapy. Due to continuing uncertainty about the benefits of treating moderate, isolated intraocular hypertension, a new, large randomized trial is now under way.[34]

The adverse effects of glaucoma treatment are potentially significant. Antiglaucoma medications must be taken for life and are accompanied by a variety of side effects. Eye drops containing cholinergic agonists (e.g., pilocarpine, carbachol, and echothiophate) and adrenergic agonists (epinephrine and dipivefrin) can cause ocular and systemic side effects; topical β blockers (e.g., timolol, levobunolol, metipranol, and betaxolol) can cause bradycardia, bronchospasm, or worsening of congestive heart failure; and oral carbonic anhydrase inhibitors (e.g., acetazolamide, methazolamide) can cause malaise, anorexia, and other adverse systemic effects.[35,36]

Argon laser trabeculoplasty appears to be a relatively safe alternative to medication, but it is expensive and its long-term effectiveness remains uncertain.[1,37] Although laser treatment lowered IOP more effectively than medications in one trial, more than half of laser-treated eyes required medications to control IOP, and no difference in progression to visual deficits was noted in 2-year follow-up.[37] Filtering surgery, which is usually reserved for patients unresponsive to other treatment, achieves greater reductions in IOP but carries a higher risk of serious postoperative ophthalmologic complications, including permanent loss of vision.[1] Trials of surgery as initial treatment for glaucoma are under way.[36]

Recommendations of Other Groups

The American Academy of Ophthalmology recommends a comprehensive eye examination by an ophthalmologist (including examination of the optic disc and tonometry) for all adults beginning around age 40, and periodic reexamination thereafter. Periodic examination every 3–5 years is

also recommended for younger black men and women (age 20–39), due to their higher risk of glaucoma.[38] The American Optometric Association recommends regular optometric evaluations (including tonometry) for all adults, and advises primary care clinicians to screen for glaucoma (with ophthalmoscopy and/or tonometry) in high-risk groups, including persons over 50, blacks, diabetics or hypertensives, relatives of glaucoma patients, and others with specific health concerns or medical conditions.[39] Prevent Blindness America (formerly the National Society to Prevent Blindness) recommends that asymptomatic individuals have periodic comprehensive eye examinations beginning at age 20, with increasing frequency for African Americans and others at high risk.[40] A 1988 review by the Office of Technology Assessment of the U.S. Congress concluded that the benefits of screening for glaucoma or ocular hypertension among the elderly were uncertain.[10] The Canadian Task Force on the Periodic Health Examination concluded there was insufficient evidence to recommend for or against screening for glaucoma in the periodic health examination, but stated that referral of high-risk persons to a specialist with access to automated perimetry was "clinically prudent."[41]

Discussion

Glaucoma remains an important cause of blindness and impaired vision in older Americans, especially among blacks. Treatment of glaucoma with medications or surgery to lower intraocular pressure has been the standard of care for many years, and it remains prudent for patients with more severe visual deficits or extreme elevations in intraocular pressure. Definitive evidence to support the benefit of treating persons with early, mild disease is not yet available, however. Controlled treatment trials currently under way may help resolve the questions about early intervention in persons with mild disease and those at increased risk for glaucoma.

Despite a potential benefit of early treatment, the current evidence is not sufficient to recommend for or against routine screening for glaucoma in the primary care setting. There is currently no efficient and reliable method for primary care clinicians to detect patients who have early glaucoma or who are likely to develop glaucoma. While patients with elevated intraocular pressure are at increased risk of developing glaucoma, the majority may never develop significant vision problems, and the benefit of early treatment for such patients remains unproven.

Accurate glaucoma screening is best performed by eye specialists with access to specialized equipment for assessing the appearance and function of the optic nerve (e.g., slit-lamp, automated perimetry). Even experts, however, face limitations in screening patients for early disease. Of the three methods currently available for screening (tonometry, examination

of the optic disk, and measurement of visual fields), only the latter is sufficiently sensitive and specific for glaucoma. Perimetry, however, is relatively expensive and time-consuming for use in routine screening, it detects patients relatively late in the disease process, and older patients may have difficulty adequately completing the examination.

Assuming that treatment of early glaucoma is effective, screening will be most useful in populations with an increased prevalence of glaucoma. If newer methods prove able to detect early and specific evidence of glaucoma (e.g., optic nerve damage), routine screening for early disease may become more feasible.

CLINICAL INTERVENTION

There is insufficient evidence to recommend for or against routine screening by primary care clinicians for elevated intraocular pressure or early glaucoma ("C" recommendation). Effective screening for glaucoma is best performed by eye specialists who have access to specialized equipment to evaluate the optic disc and measure visual fields. Recommendations may be made on other grounds to refer high-risk patients for evaluation by eye specialists. This recommendation is based on the substantial prevalence of unrecognized glaucoma in these populations, the progressive nature of untreated disease, and expert consensus that reducing intraocular pressure may slow the rate of visual loss in patients with early glaucoma or severe intraocular hypertension. Populations in whom the prevalence of glaucoma is greater than 1% include blacks over age 40 and whites over age 65. Patients with a family history of glaucoma, patients with diabetes, and patients with severe myopia are also at increased risk and may benefit from screening. The optimal frequency for glaucoma screening has not been determined and is left to clinical discretion.

The draft update of this chapter was prepared for the U.S. Preventive Services Task Force by David Atkins, MD, MPH, with contributions from materials prepared by Christopher Patterson, MD, FRCP, for the Canadian Task Force on the Periodic Health Examination.

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