

Evaluation of the Glaucoma Suspect

Using clinical data to make treatment decisions.

BY EYDIE MILLER, MD

Evaluating a patient with a possible diagnosis of glaucoma is a challenge. A glaucoma suspect is an individual who is at risk of losing visual function from glaucoma but in whom glaucomatous damage is not clearly evident.¹ The term *glaucoma suspect* refers to a situation where the angle is open on gonioscopy and there is an absence of secondary causes of glaucoma such as pigment dispersion syndrome, pseudoexfoliation, inflammation, or trauma. An individual can be classified as a glaucoma suspect based on an elevated IOP (ocular hypertension), a suspicious optic disc appearance, a suspicious visual field, significant risk factors, or a combination thereof.

RISK FACTORS

Ophthalmologists have long recognized ocular hypertension (IOP > 21 mm Hg) as a risk factor for glaucoma. Other factors include African American race, a family history of glaucoma, and advanced age.¹ The Ocular Hypertension Treatment Study² helped define baseline factors that increase the risk of converting to glaucoma in eyes in which the pressure is elevated and the optic disc and visual field are normal. Those risk factors include a central corneal thickness of < 556 μ m, a C/D > 0.4, and a larger-than-average pattern standard deviation on an otherwise normal threshold visual field.³ Additional ocular and systemic risk factors are diabetes, hypertension, high myopia, cardiovascular disease, and migraine/vasospasm, all of which the practitioner must take into account.¹

OPTIC DISC

When considering the disc itself, clinicians may become alert to the possibility of glaucoma owing to certain features. Increased cupping (diffuse or focal narrowing of the disc rim), asymmetric cupping, and recurrent disc hemorrhages are classic high-risk findings. Additionally, other disc types exist where the overlap

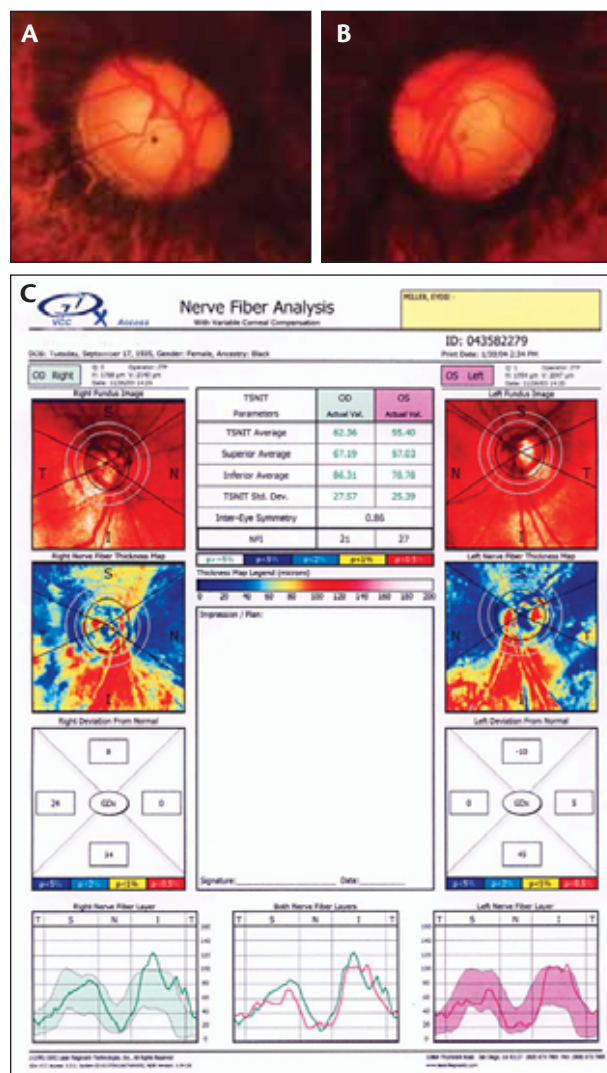


Figure 1. This patient had tilted, myopic discs with thinning of the temporal rims (A, B). Imaging with the GDx VCC showed normal NFL thickness but mild superior flattening consistent with tilted discs.

between glaucomatous and nonglaucomatous discs is greater, such as occurs with tilted discs, large optic nerve heads with thin disc rims, and anomalous discs.

Traditionally, clinicians have used stereo photography both for documenting the baseline optic disc appearance and for follow-up. This technique is not useful for distinguishing glaucomatous from nonglaucomatous nerves at baseline, however. Recently, computerized optic disc imaging devices have been used for both baseline evaluation and the follow-up of discs. Practitioners have had limited success with these instruments in separating normal eyes from those with early glaucoma, but these devices provide valuable information that, in combination with other clinical information, can be quite helpful in identifying susceptible individuals.⁴⁻⁶ The two devices my colleagues and I use in our practice are confocal scanning laser tomography with the Heidelberg Retinal Tomograph (HRT; Heidelberg Engineering GmbH, Dossenheim, Germany) and nerve fiber layer (NFL) polarimetry with the GDx VCC (Laser Diagnostic Technologies, San Diego, CA).

PERIMETRY

Practitioners typically assess a patient's visual field with white-on-white threshold automated perimetry. A normal field does not preclude a diagnosis of glaucoma, however, because structural optic disc atrophy precedes field loss on standard threshold perimetry.⁷ Thus, other methods have been developed to assess "pre-perimetric" glaucoma.

Automated perimetric strategies that test a smaller subpopulation of retinal ganglion cells have the potential to detect visual field loss earlier. The tests we use in our practice are short wavelength automated perimetry (SWAP; Carl Zeiss Meditec Inc., Dublin, CA) and frequency doubling technology (Welch Allyn Medical Products, Skaneateles, NY). Various studies have shown that these methods may be able to detect visual field defects that predate those on standard perimetry by 3 to 5 years or to confirm questionable defects on standard perimetry.^{8,9} One of the drawbacks of SWAP is the test's variability. It is therefore important that patients who are familiar with perimetric testing and who have performed well on previous white-on-white testing be considered for these versions of functional testing. Furthermore, practitioners must confirm defects prior to initiating or escalating therapy.

PATIENT EVALUATION

The typical patient who is being evaluated as a glaucoma suspect has mixed clinical findings. The goal of the initial examination is to gather as much data as pos-

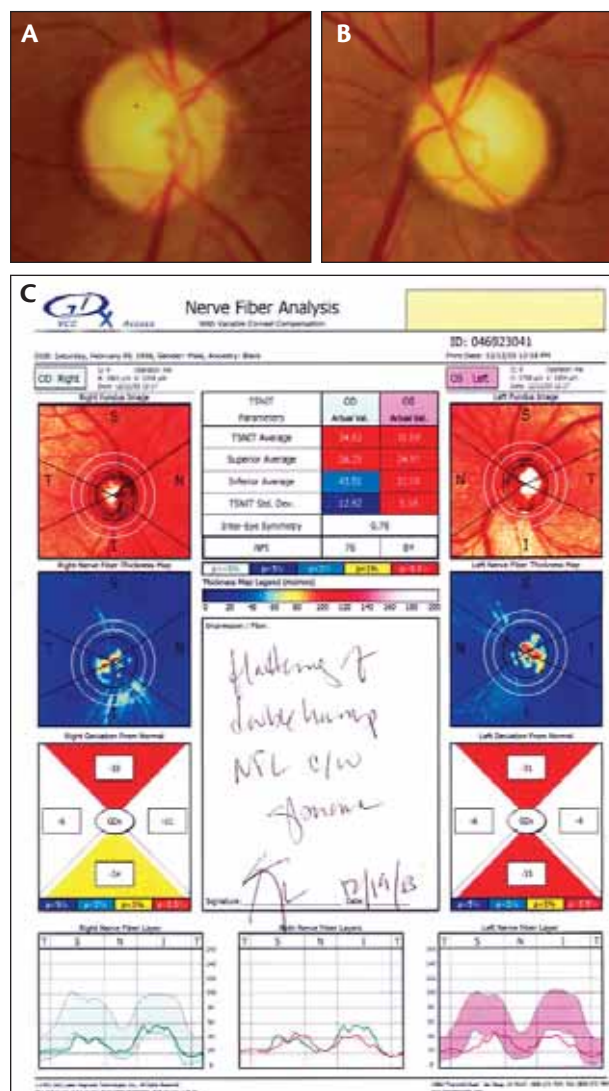


Figure 2. This patient exhibited mild cupping in his right eye (A) and moderate cupping with a thin superior rim in his left (B). Imaging with the GDx VCC showed pronounced NFL loss at the superior and inferior poles of the optic disc (C).

sible and to document the patient's baseline status. Based on these findings, the practitioner either prescribes treatment or follows the patient. Following are some examples of patients from my practice.

Case 1: Recurrent Disc Hemorrhages

A 57-year-old white male presented in 1995 with 20/15 UCVA OU and mild ocular hypertension. His IOP ranged between 23 and 26 mm Hg, his discs had a healthy appearance with a C/D ratio of 0.2, and his fields were normal on standard threshold perimetry. I obtained optic disc photos to document baseline and

followed the patient. When he later developed a disc hemorrhage in his right eye, I initiated treatment that resulted in an IOP of 18 mm Hg OU.

Over the next 3 years, the patient's IOP gradually crept up to 22 mm Hg OU, and I observed another disc hemorrhage in his right eye. HRT and SWAP results were normal, but the presence of the hemorrhage prompted me to increase his medication in order to regain an IOP of 18 mm Hg OU.

In 2002, another disc hemorrhage occurred despite an IOP of 18 mm Hg OU. The HRT and SWAP findings were unchanged. By this time, our practice had begun using pachymetry, and I measured the patient's central corneal thickness at 502 μ m OD and 505 μ m OS. The thinness of the patient's corneas indicated that Goldmann applanation tonometry underestimated his IOP. I adjusted the patient's treatment to reach a target IOP in the mid-to-low teens. Thus far, I have noted no additional disc hemorrhages, and the results with SWAP and HRT have remained unchanged.

Case 2: Myopic Discs

A 66-year-old black female presented in 1990 with high myopia (-13.00 D OD and -10.50 D OS), 20/25 BCVA OU, a positive family history of glaucoma, and mild hypertension. Her IOP was in the midteens bilaterally, and a tilted disc with a posterior staphyloma was present in each eye (Figure 1A and B). I obtained baseline disc photos and threshold automated perimetry and found nonspecific changes on the field. Treatment was not initiated.

By 2003, the patient's BCVA had declined to 20/50 OU due to cataracts. On examination, her IOP remained stable, but her discs seemed more cupped compared to the baseline photos. New disc photos were obtained, and a photo-to-photo comparison showed a stable optic disc appearance. Cataract surgery resulted in 20/25 UCVA OU. Perimetry still demonstrated nonspecific loss, but the NFL evaluation using the GDx VCC was within the normal acceptable range (Figure 1C). The central corneal thickness was normal at 553 μ m OD and 556 μ m OS. The patient continues to be followed without treatment.

Case 3: Disc Cupping, Normal IOP

A 67-year-old black male with hypertension, adult-onset diabetes, a negative family history of glaucoma, and an exotropia with mild amblyopia in his left eye presented for a routine examination in 1999. His BCVA was 20/20 OD and 20/30 OS, and his IOP measured 12 mm Hg OD and 14 mm Hg OS. Suspicious disc cupping was present (Figure 2A and B), and the fields were

borderline, especially in the patient's left eye due to his inability to maintain fixation. I obtained baseline disc photos.

By 2003, the patient's IOP had increased to between 13 and 17 mm Hg OD and between 16 and 20 mm Hg OS. I obtained new disc photos, which were stable compared to the baseline set. Repeat Humphrey Visual Field testing (Carl Zeiss Meditec Inc.) showed stability in his right eye but was unreliable in his left. Pachymetry measurements revealed thin central corneas (474 μ m OD, 470 μ m OS), and GDx VCC testing showed very thin NFLs bilaterally (Figure 2C). I initiated treatment.

Case 4: Ocular Hypertension, Small Optic Nerve Heads

A 59-year-old white female with mild ocular hypertension presented for a second opinion regarding her need for glaucoma medication. She had a negative family history of glaucoma. Her medical history was remarkable for asthma and hypertension. Her UCVA was 20/25 OU, and her untreated IOP ranged from 22 to 25 mm Hg OD and from 20 to 24 mm Hg OS. She had small,

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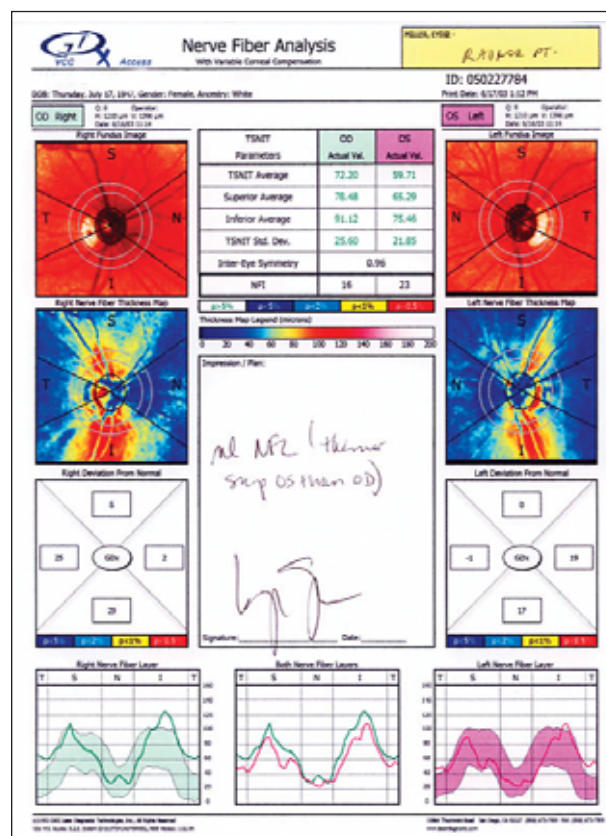


Figure 3. Imaging with the GDx VCC showed a normal NFL that was slightly thinner in this patient's left eye.

Reappraising the Safety of Beta-Blocker Therapy for Glaucoma

Evidence from scientific data debunks some long-held beliefs.

BY PAUL J. LAMA, MD

Ophthalmic beta-adrenergic blockers have been important in the management of glaucoma and ocular hypertension. These agents are second to prostaglandin analogues in efficacy, and they have unsurpassed ocular tolerability. In addition, investigations such as the Ocular Hypertension Treatment Study¹ have shown that more than half of patients on medical glaucoma therapy will need multi-agent treatment. The use of beta-blockers, whether first-line or adjunctive, will therefore likely be inescapable.

Despite beta-blockers' efficacy and local tolerability, practitioners have become increasingly concerned that these agents' chronic use could result in potentially serious systemic side effects. The complete and indiscriminate avoidance of beta-blocker therapy, however, ignores a substantial proportion of patients who may benefit from these agents. It is therefore incumbent upon the clinician to know beta-blockers' potential systemic interactions as evident from scientifically available data rather than unproven dogma or non-peer-reviewed sources, especially those peddled by competing pharmaceutical companies.

CARDIOVASCULAR DISEASE

Beta-blockers have long played an integral role in the management of cardiovascular disease, but, traditionally, medical education has held that these agents should be avoided in patients with congestive heart failure (CHF) and symptomatic bradycardia as well as more advanced degrees of heart block. Recent data from randomized placebo-controlled trials, however, prove that beta-blockers actually benefit patients with compensated heart failure.²⁻⁸ The evidence demonstrating a reduction in mortality and improved functional status is incontrovertible. In fact, even patients with the most advanced degrees of heart failure, including some awaiting heart transplantation, may benefit from beta-blocker therapy.²

"We now know that certain heart conditions not only do not preclude beta-blocker therapy but actually necessitate it."

The American College of Cardiology currently recommends that all patients with depressed left ventricular function, when clinically stable, begin beta-blocker therapy, regardless of whether or not they had a myocardial infarction.²⁻⁸ Studies conducted more than 20 years ago showed that all patients who have suffered myocardial infarction should undergo beta-blocker therapy for at least 3 years.⁹⁻¹¹

How does this information affect ophthalmologists? First, we now know that certain heart conditions not only do not preclude beta-blocker therapy but actually necessitate it. Second, because patients on systemic beta-blockers will have plasma levels of the drug far greater than those achieved by topical administration, concomitant topical administration will not appreciably affect their total plasma levels. Initiating beta-blockers for glaucoma, therefore, will neither interfere in the management of patients' underlying cardiac condition nor appreciably increase their risk of dose-related toxicity. No data are available regarding whether the beta-blockers approved for the treatment of CHF affect aqueous production, thus negating the IOP-lowering effect of ophthalmically administered beta-blockers.

PULMONARY DISEASE

Asthma affects roughly 5% of the US population. Recurrent episodes of airway obstruction with periods of essentially normal lung function are characteristic of this

syndrome. Affected individuals demonstrate hyperresponsiveness to stimuli that have little or no effect in normal individuals.¹¹ During an attack, airway resistance increases at all levels. Spirometric changes occur, as demonstrated by a reduction in the peak expiratory flow rate, 1-second forced expiratory volume (FEV1), and maximal mid-expiratory flow rate.¹² Blockade of beta-adrenergic receptors—specifically the beta-2 subtype—may precipitate or potentiate an attack. In fact, several case reports have described beta-adrenergic blocker-induced bronchospasm leading to death.¹³ Nonfatal attacks have also been reported. Interestingly, in the nonfatal attacks, the degree of pulmonary obstruction was unpredictable.¹³ It is thus apparent that small doses can trigger an attack or affect airway resistance.

A study comparing timolol with placebo eye drops in 15 asthmatics and 10 nonasthmatics demonstrated a drop in FEV1 in 13 of 15 asthmatics.¹⁴ In four of these individuals, the reduction exceeded 20%. Although a 20% reduction in FEV1 is clinically significant, such a change follows acute administration of the drug, and the long-term effects of beta-adrenergic blockers on FEV1 may not necessarily be constant. Salpeter et al¹⁵ performed a meta-analysis of 29 clinical trials studying acute (single dose) and chronic (up to 4 weeks) systemic administration of beta-1 selective beta-blockers in patients with mild-to-moderate asthma and in patients with chronic obstructive pulmonary disease (COPD). The investigators found that acute administration caused a drop in FEV1 by 7.46% versus no effect on FEV1 from chronic administration of up to 4 weeks in asthmatics. This finding may be due to an upregulation of beta-2 receptors after chronic administration. Individuals with COPD did not experience a change in FEV1 when the agent was administered acutely or chronically.

Although such data suggest that internists may safely prescribe a systemic beta-1 selective beta-blocker for patients with controlled, mild-to-moderate asthma or COPD and a history of myocardial infarction or CHF because of the agent's life-saving potential, they do not imply that topical nonselective beta-blocker therapy is not potentially harmful to patients with asthma or COPD. Glaucoma patients with concomitant pulmonary disease, therefore, generally should not receive these agents until further data are available from randomized, placebo-controlled, clinical trials that look specifically at topical administration in these conditions.

DEPRESSION

The association between beta-blockers and depression is largely based on published case reports and short case series.¹⁶ By contrast, the cumulative evidence from prospective placebo-controlled clinical trials, case-controlled

studies, and large population-based surveys of patients receiving systemic beta-blocker therapy overwhelmingly failed to identify such an association.¹⁶ Many of these studies concluded that beta-blockers, as a group, pose no greater risk of causing depression than other antihypertensive agents not known to be associated with depression. More specifically, 16 of 19 studies failed to support this association; three of them were randomized prospective clinical trials involving moderate-to-high doses of oral agents.

OTHER CLINICAL SITUATIONS

Overall, either the literature fails to support many of the traditionally cited negative effects of beta-blockers, including worsening symptoms of peripheral vascular disease (ie, intermittent claudication or prolonged hypoglycemia in type II diabetics), or there exists only supportive evidence when beta-blockers are administered systemically.^{17,18} For example, systemic doses of beta-blockers have been shown to reduce individuals' exercise tolerance and exercise work output. These effects are not simply the result of a reduction in heart rate or blood pressure, such as ophthalmic doses may cause during exercise, but are due to complex alterations in energy and electrolyte metabolism.¹⁹⁻²² Dickstein et al^{23,24} demonstrated that timolol solution, timolol gellan, and betaxolol reduce the heart rate and systolic arterial blood pressure at baseline and during exercise (the effect on the heart rate was statistically more significant than the effect on systolic arterial blood pressure), but they found no difference in work output. These data provide additional support for the concepts that heart rate and blood pressure alone do not account for differences in exercise capacity and that ophthalmically administered doses may be insufficient to affect work output, despite the statistically significant changes in hemodynamic parameters.

FINAL THOUGHTS

Ophthalmic beta-blockers are an important part of the glaucoma pharmacological armamentarium. The call for more aggressive IOP control makes the need for combination drug therapy inescapable, despite the advent of potent prostaglandin agents. Rather than summarily avoid beta-blockers as a class due to often unwarranted fears about triggering unwanted systemic side-effects and the associated risks of litigation, ophthalmologists need to reappraise the role of these agents in the management of glaucoma. This reassessment should involve evidence-based data instead of traditional dogma. Numerous individuals may achieve a significant therapeutic response with this form of treatment, and the available evidence suggests that many patients previously considered to be

inappropriate candidates for beta-blocker therapy can safely take these agents. Patients with asthma, symptomatic bradycardia, or newly diagnosed nonphysiologic bradycardia should not receive an ophthalmic beta-blocker, however. □

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cupless optic nerve heads and borderline threshold visual fields.

The patient began treatment in 2000 but ceased it 2 years later due to multiple medication intolerances. Further evaluation with frequency doubling technology showed borderline visual field changes. Imaging with the GDx VCC found that her NFLs were within an acceptable, normal range, although thinner in her left eye (Figure 3). Pachymetry measured 599 μ m OD and 595 μ m OS. The patient was followed without treatment.

SUMMARY

There often is no correct answer on whether to treat a patient who is a glaucoma suspect. The clinician must assess individual risk factors, obtain good baseline studies, and discuss treatment options with the patient. The risk of glaucomatous damage must be balanced with the risk and cost of treatment. Because most glaucomatous changes will occur slowly, it is not imperative to make a treatment decision on the patient's first visit. Continued surveillance and regular follow-up is important, however, because the preservation of patients' vision is the practitioner's ultimate goal. □

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