The "Well-Controlled" but Progressing Glaucoma Patient

What to consider when faced with such an individual.

BY TONY REALINI, MD

The reality of glaucoma management is that we practitioners control, but do not cure, glaucoma by lowering patients' IOP. When we speak of the *well-controlled patient*, we imply that the disease is well controlled, but we are often simply referring to the patient's IOP during the office visit. Such statements are misleading, because we can only determine the adequacy of a patient's IOP control in retrospect; in other words, the IOP was well controlled if the patient's disease did not progress.

The topic of control is relevant because some patients deemed to have well-controlled IOP go blind from their glaucoma. Researchers at the Mayo Clinic found that patients treated for glaucoma have a 27% risk of unilateral blindness and a 9% risk of bilateral blindness at 20 years.[1] Investigators at the University of Seattle reported the slightly more promising numbers of 14.6% for unilateral blindness and 6.4% for bilateral blindness, but their follow-up period was only 15 years.[2] It is highly unlikely that the majority of these studies' subjects were poorly managed. Instead, many probably seemed to have well-controlled IOP but still went blind. Clinical trials bear out this supposition. In the Ocular Hypertension Treatment Study, 5% of subjects developed glaucoma despite a 20% IOP reduction.[3] Disease progression occurred in 12% of patients enrolled in the Collaborative Normal-Tension Glaucoma Study (CNTGS) in spite of a 30% IOP reduction,[4] and 45% of patients in the Early Manifest Glaucoma Trial experienced disease progression despite an average IOP reduction of 25% via laser trabeculoplasty and b.i.d. topical beta-blocker therapy.[5]

This article reviews several issues worth considering when treating patients whose glaucomatous optic neuropathy is progressing regardless of seemingly well-controlled IOP.

CORNEAL THICKNESS

By now, all practitioners are aware of the Ocular Hypertension Treatment Study finding that central corneal thickness is the single strongest predictor of the conversion of ocular hypertension to glaucoma.[6] Because central corneal thickness affects the accuracy of IOP measurements, the Goldmann tonometer's tip was designed to neutralize artifact from corneas of average thickness. The artifact is not completely neutralized in eyes with corneas that are thinner or thicker than average, however. For reference, ultrasound pachymetry measures average corneal thickness at approximately 550 µm. Thick corneas result in overestimations of true IOP, whereas thin corneas yield underestimations.

Most of us manage glaucoma by setting a target pressure—a process that is far more gestalt than mathematics.[7] Now, of course, many of us measure central corneal thickness as a standard part of the glaucoma work-up, and we add the data to our calculations of target pressure. Knowing the corneal thickness of a well-controlled but progressing patient is critical. A thin cornea can fool us into believing that a patient's IOP is better controlled than it is.

Rectifying this problem is easy. Simply measure central corneal thickness in progressing patients. If the value is low, consider lowering the therapeutic IOP target. Unfortunately, there is no established means of calculating a "true" IOP with the Goldmann tonometry reading and the corneal thickness measurement. Nonetheless, it is likely that, the thinner the cornea is, the greater the underestimation produced by Goldmann tonometry will be.

DIURNAL IOP VARIABILITY

Daily Fluctuations

IOP is a dynamic variable that changes continuously. Various studies have reported that eyes with untreated

glaucoma can manifest daily IOP fluctuations of as great as 10 to 15 mm Hg; treatment reduces these variations to between 6 and 8 mm Hg, in contrast to the 3 to 4 mm Hg of variability observed in normal eyes over the course of a day.[8,9]

Diurnal variation can explain progression in some patients with seemingly well-controlled IOP. Like most people, our patients fall into certain habits, one of which is a tendency to schedule their eye appointments for roughly the same time. As a result, you may see the same patient at midmorning every 3 months for 5 years. His IOP may be on target at every visit, but that could be because his IOP is at the bottom of his diurnal curve at this time of day. The patient's IOP could be 7 mm Hg higher at another time of day. If you never check his IOP at any time other than midmorning, you will never discover this pressure fluctuation, which has been shown to be a risk factor for progressive optic neuropathy.[10]

Drug Efficacy

A related source of progression arises from the variable IOP-lowering efficacy exhibited by some drugs over their dosing period. For instance, a twice-daily drug may have peak IOP-lowering efficacy 2 hours after dosing and trough IOP efficacy at the end of the dosing interval. If a patient instills his drops at 8:00 AM every morning and regularly visits your office at midmorning, you will measure his IOP at its lowest level and miss information from the period of time when his drug is wearing off. For some therapeutic agents, the difference between peak and trough efficacy can be as great as 3 to 4 mm Hg, an amount that can make the difference between stability and progression.

The key to identifying both diurnal issues and peak-trough efficacy issues is to keep scheduling trends in mind. During the course of a busy day in the clinic, keeping track of your patients' usual appointment times is unlikely to be foremost in your mind. I make a point of noting in patients' charts the times when I take their IOP measurements. By simply flipping through a few pages, I can quickly determine if a given patient generally comes to the office at the same time of day for every appointment. In such cases, I ask him to choose a different time for his next appointment and explain why. More than once, I have been unpleasantly surprised by high IOP measurements during these follow-up visits and have had to adjust the therapeutic plan to provide better diurnal IOP control or trough IOP coverage.

NONCOMPLIANCE

Noncompliance can take many forms. Some patients lead you to believe that their IOP is better controlled than it really is by only taking their medications immediately before their appointments. For 1 day out of every 3 or 4 months, their IOP is excellent, and you are fooled into believing that this IOP measurement is representative of the other 100 or so days in between visits. Patients may behave in this fashion for a number of reasons. The drugs may have side effects that the patients find intolerable, or perhaps they cannot afford their medications on a daily basis. Regardless of the motivation, the bigger problem is that patients do not voluntarily admit to their noncompliance and often will not come clean even under direct questioning.

Because it is difficult to prove, noncompliance is hard to remedy. A call to the patient's pharmacy can reveal long gaps between drug refills. If a family member is present in the examination room with a patient, I will occasionally casually ask, "Does your husband remember his eye drops regularly?" If these nonconfrontational attempts fail, however, you have little recourse beyond counseling your patients on the importance of compliance and hoping that they see the light.

NON-IOP DISEASE MECHANISMS

We do not know what causes glaucoma. Elevated IOP is a risk factor for the disease, and we treat glaucoma by practicing risk factor modification. Specifically, we lower patients' IOP, but elevated pressure is only one of several risk factors. The AAO now defines primary open-angle glaucoma as a "multifactorial optic neuropathy."[11] Unfortunately, we have not firmly established what glaucoma patients' other risk factors may be, how to identify those who have them, or how to treat such individuals if we could identify them.

The purpose of this article is not to thoroughly discuss the details of potential non-IOP mechanisms of glaucomatous optic neuropathy. Although we cannot do much about them, remembering that these mechanisms very likely exist can impact our management of the disease. For instance, consider one patient of mine with progressing glaucoma who has an untreated IOP of 12 mm Hg OU and bilateral corneal pachymetry measurements of 550 µm. Her optic nerves have 0.9 cups, and her visual fields show bilateral superior arcuate defects. On three topical medications, her IOP only drops to 11 mm Hg.

According to the criteria of the CNTGS, my patient warrants a 30% IOP reduction, which, in her case, can only be achieved with surgery. Before you schedule her for trabeculectomy with mitomycin C, however, consider that her hands are always ice-cold when I greet her. In addition, she has a disc hemorrhage on each optic nerve and suffers chronic migraine headaches.

Although this patient has classic normal-tension glau-

coma, in my opinion, the damage to her optic nerves is not the result of IOP, but rather may be due to some form of vasculopathy. She likely has an IOP-independent disease, and glaucoma surgery may not help her. The ideal treatment for this type of patient is not clear at present. The most recent analysis from the CNTGS Group demonstrated that, in vasculopathic patients such as this one, IOP reduction is not beneficial in controlling the optic neuropathy.[12] Although not a perfect analysis by any means, the new CNTGS data underscore how little we know about treating normal-tension glaucoma. As frustrating as it is, I am likely to do more harm than good by operating on this patient, who has no evidence of pressure-related damage, and I do not want to hurt her.

CONCLUSION

Some patients with apparently well-controlled IOP experience glaucomatous progression. Clearly, certain individuals simply need a lower target IOP than we initially thought, and we should remember that target IOPs are only educated guesses. With other patients, however, issues such as noncompliance, diurnal fluctuations, and thin corneas can lull us into a false sense of security regarding their IOP control. Carefully evaluating these individuals often reveals the reason for the apparent mismatch between their IOP control and disease progression. ❑

Tony Realini, MD, is Associate Professor of Ophthalmology at West Virginia University Eye Institute in Morgantown, West Virginia. Dr. Realini may be reached at (304) 598-6926; hypotony@yahoo.com.

1. Hattenhauer MG, Johnson DH, Ing HH, et al. The probability of blindness from open-angle glaucoma. *Ophthalmology.* 1998;105:2099-2104.
2. Chen PP. Blindness in patients with treated open-angle glaucoma. *Ophthalmology.* 2003;110:726-733.
3. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol.* 2002;120:701-713.
4. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Collaborative Normal-Tension Glaucoma Study Group. *Am J Ophthalmol.* 1998;126:487-497.
5. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol.* 2002;120:1268-1279.
6. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol.* 2002;120:714-720.
7. Realini T, Fechtner RD. Target intraocular pressure in glaucoma management. *Ophthal Clin N Amer.* 2000;13:407-415.
8. Drance SM. The significance of the diurnal tension variations in normal and glaucomatous eyes. *Arch Ophthalmol.* 1960;64:494-501.
9. Drance SM. Diurnal variation of intraocular pressure in treated glaucoma: significance in patients with chronic simple glaucoma. *Arch Ophthalmol.* 1963;70:302-311.
10. Asrani SG, Zeimer R, Wilensky J, et al. Large diurnal fluctuations in IOP are an independent risk factor in glaucoma patients. *J Glaucoma.* 2000;9:134-142.
11. American Academy of Ophthalmology. *Preferred Practice Patterns: Primary Open-Angle Glaucoma.* San Francisco, CA: American Academy of Ophthalmology; 2000.
12. Anderson DR, Drance SM, Schulzer M. Factors that predict the benefit of lowering intraocular pressure in normal tension glaucoma. *Am J Ophthalmol.* 2003;136:820-829.