MANAGING NORMAL-TENSION GLAUCOMA

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A common clinical encounter at a Hawaiian practice.

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Normal-tension glaucoma (NTG) is a common clinical encounter at my practice in Honolulu, affecting 65% of the glaucoma patients I see. Treating NTG can be challenging because it is likely a catch-all term for a variety of disease mechanisms, but doing so provides me with a rewarding opportunity to collaborate with patients on their care. This article details how NTG presents in my practice and my thought process on disease management.

PATIENT POPULATION

My glaucoma and comprehensive patient panel composition is about 28% White, 19% Japanese, 11% Filipino, 11% Native Hawaiian, 8% Chinese, 10% other Asian or Pacific Islander, 5% Hispanic, and 4% Black. Of my patients with NTG, 56% are Japanese, 14% are White, 10% are Filipino, 10% are Chinese, and 10% are Hawaiian. These NTG patients range from 45 to 97 years old, with a median age of 77 years. Interestingly, 70% are female, in contrast to my entire patient panel, which is 53% female.

PHENOTYPE

By the time patients with NTG arrive at my clinic, their disease is usually moderate to severe. I suspect a patient has NTG if they meet the criteria for primary open-angle glaucoma (POAG), such as an open angle and progressive cupping from retinal nerve fiber layer loss with corresponding visual field defects, but IOP is below 22 mm Hg. I do not make a corrective adjustment to the IOP for thin central corneal thickness, but I recognize that a thin cornea may lead to a falsely low IOP reading. When feasible, I recommend patients perform a short period of home IOP monitoring to look for diurnal variation. If the patient has high IOP spikes (typically seen in the morning or at night), I determine whether they truly have NTG or if it is POAG. I obtain a thorough history to rule out other causes of optic neuropathy, such as prior trauma, episodes of severe eye pain that might indicate prior inflammation, and steroid use.

When making a diagnosis, I look for classic visual field defects, focal retinal nerve fiber layer loss, and optic nerve pits and hemorrhages to help determine if the optic neuropathy is truly glaucomatous. I perform further neuroimaging and lab workup when I suspect other culprits causing optic neuropathy. This typically happens when the patient is younger than 50 years, has nerve pallor, has low visual acuity, or has a visual field defect that respects the vertical midline. Testing may include MRI, an antinuclear body panel, a syphilis antibody panel, vitamin B12 and B9 levels, and a heavy metal panel. In the past 2 years, I have identified three patients with high mercury levels (all of whom ate fish several times per day) and one patient with a high lead level.

If I suspect a diagnosis of NTG, I complete a focused investigation of the patient's systemic disease and past ocular history. Many of my patients with NTG administer blood pressure–lowering medication and a statin and/or use a continuous positive airway pressure machine for obstructive sleep apnea without associated obesity. Given the large East Asian population, many of my patients present with a diagnosis of NTG and high myopia and corresponding posterior pole signs of myopic degeneration. Anecdotally, I also have a small group of patients with Alzheimer disease whose NTG seems particularly resistant to treatment, possibly related to vascular dysregulation. Where I practice, migraines, Flammer syndrome, and Raynaud syndrome are rare among patients with NTG, despite the associations reported in the literature.

PROGRESSION

My patients with NTG seem to fall into two broad categories: (1) those whose visual field defects do not become visually significant over decades on minimal to no treatment and (2) those whose disease worsens precipitously despite maximum medical therapy and surgical intervention. Many patients I see have stable disease for years on one or

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two classes of IOP-lowering drops. These patients may have never progressed to a visually significant level even without treatment, but they often prefer to stay on their medication when offered a drop holiday. In addition, when these "stable" patients start to demonstrate slow disease progression, it typically coincides with when they undergo cataract surgery combined with MIGS. This generally provides them with additional years of disease stability.

I monitor a small subset of patients with NTG for disease progression without treatment, either because of patient preference or because their testing and exam findings are stable. These patients may eventually require intervention, usually when they develop more systemic failure such as vascular compromise, which seems to speed up the rate of optic nerve damage; however, 5 to 10 years could elapse before any intervention is needed.

MANAGEMENT

With so many unknowns about the pathophysiology of NTG, I see it as my mission to develop several hypotheses for why a patient has NTG by mining for modifiable systemic associations. Does the patient administer blood pressure medication? If so, at what time of day? Do they feel dizzy when they stand up from a seated position? If they have asymmetric glaucoma, which side of their body do they sleep on at night? If I suspect vascular dysregulation, I ask the patient to measure their blood pressure several times throughout the day while lying down, sitting, and standing. When possible, I work with their primary care physician to address conditions such as hypotension, obstructive sleep apnea, atrial fibrillation, and anemia. Although it is unclear if these measures ultimately affect visual outcomes, they are easy to execute and can motivate the patient to improve their overall health.

In accordance with the results of the Collaborative Normal Tension Glaucoma Study (CNTGS), I focus on reducing IOP by 30% from baseline if a patient demonstrates progression.[1] If the patient's IOP is in the midteens or higher, I offer selective laser trabeculoplasty as a first-line option to reduce diurnal IOP fluctuation and lower the risk of disease progression. If the patient continues to demonstrate progression or if the starting IOPs were already in the low teens, my agent of choice is brimonidine, which may have neuroprotective qualities. This decision is based on the findings of the Low-Pressure Glaucoma Treatment Study (LOGTS), which compared brimonidine with timolol as first-line therapy and found that patients treated with the former were less likely to experience visual field progression.[2]

I quickly transition to surgical intervention if disease progression continues after the initiation of therapy with one or two classes of glaucoma medication or if a 30% reduction in IOP is not achieved. With worsening paracentral defects, there is less time for monitoring and a greater need for action. Patients whose disease is progressing return more frequently for testing, treatment changes, and conversations about potential surgery. I will alternate between 24-2 and 10-2 visual field testing strategies to develop a more granular understanding of a patient's disease progression and to help them appreciate their need for surgery based on the evolution of their visual field defects. If the patient is phakic and reliably attends their clinic visits, I begin with combined cataract surgery and MIGS and perform postoperative home IOP monitoring. If the patient continues to have diurnal variation or if there is continued progression on testing, I promptly move on to filtering surgery, usually trabeculectomy. If I believe I only have one chance for surgery in a patient, I will do a combined cataract and filtering procedure or standalone filtering surgery.

Despite these measures, I often remind myself that treating NTG is not all about reducing IOP. In fact, I sometimes suggest incrementally reducing a patient's medication load if they presented to my clinic on medical therapy but their disease seems stable on testing. Patients who do not tolerate their medications or who have difficulty remembering to administer their drops are usually elated at this suggestion and sometimes do well with no drops.

CONCLUSION

I tailor my approach to NTG treatment to the individual. One patient may have a clear systemic association, whereas another may have no modifiable risk factors other than IOP. Some patients' disease never progresses, whereas others experience rapid structural and functional deterioration over a few months. Treating NTG can be challenging, but it is rewarding to collaborate with the patient to find a solution that works for them. ■

1. 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(4):487-497.
2. Krupin T, Liebmann JM, Greenfield DS, Rosenberg LF, Ritch R, Gardiner S; Low-Pressure Glaucoma Study Group. A randomized trial of brimonidine versus timolol in preserving visual function: results from the Low-Pressure Glaucoma Treatment Study. *Am J Ophthalmol.* 2011;151(4):671-681.

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