Normal-Tension Glaucoma

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CASE PRESENTATION

In 1999, a 55-year-old white female with large cups in both eyes presented to us for glaucoma evaluation. The patient's past medical history was significant for goiter and migraine, and she had a strong family history of glaucoma; her mother and two maternal aunts had been diagnosed with the disease. The patient had smoked two packs of cigarettes per day for years. She denied a history of Raynaud’s phenomenon and other vascular disorders.

Upon presentation, the patient’s IOP measured 18 mm Hg OD and 19 mm Hg OS. The angles of both her eyes were open to the ciliary body band. The patient’s corneal pachymetry measurements were 574 µm OD and 585 µm OS, and the cup-to-disc ratios were 0.5 OD and 0.4 OS (Figure 1). The right eye had a disc hemorrhage, which is not visible in the figure provided herein. Visual field examination revealed superior arcuate defects that were worse in the patient’s left eye. A diurnal pressure curve yielded morning readings of 19 mm Hg OU. We diagnosed normal-tension glaucoma (NTG) and prescribed, at that time, Timoptic (Merck & Co., Inc., West Point, PA). In 2001, fundus examination showed disc hemorrhage, indicating progression despite an IOP of 14 mm Hg OU, and we added Lumigan (Allergan, Inc., Irvine, CA) to her drug regimen. Over the following 2 years, the patient’s visual field defects and optic nerve cupping progressed despite the addition of Alphagan (Allergan, Inc.) and a well-controlled IOP (target IOP <14 mm Hg) (Figures 2 through 4).

HOW WOULD YOU PROCEED?

1. Based on the Humphrey visual fields (Carl Zeiss Meditec, Inc., Dublin, CA) and the appearance of the optic nerve head (ONH), is there truly progression?
2. Which parameters would you use to determine if there were glaucomatous progression?
3. How would you manage this patient?
4. How would imaging with the Heidelberg Retina Tomograph (HRT; Heidelberg Engineering GmbH, Dossenheim, Germany) or Optical Coherence Tomography (OCT; Carl Zeiss Meditec, Inc.) affect your decision?
5. Does smoking play a role in this patient’s disease?
6. Should you perform further systemic work-up? If so, what?

Figure 1. The patient’s optic nerves at presentation displayed mild glaucomatous damage with cup-to-disc ratios of 0.5 OD (A) and 0.4 OS (B). There was a disc hemorrhage that is not visible on this photograph of her right eye.
In October 2003, we imaged the patient with HRT and OCT (Figures 5 and 6). Inferior, temporal, and superior thinning on OCT and superior thinning on HRT in the patient’s right eye correlated with the inferior arcuate defect and superior nasal step shown on Humphrey Visual Field testing. Inferior, nasal, and superior thinning on OCT correlated with the dense superior arcuate defect in her left eye. The HRT results may have been less reliable for this eye due to its large cup and tilted optic nerve. These results demonstrated that, despite a reduction of at least 30% in IOP, there was progression of glaucomatous damage.

The pathogenesis of NTG remains controversial, but most theories fall into the categories of either vascular or mechanical factors.1-3 Treating the disease is difficult, owing to the nebulous nature of its pathogenesis. Lowering IOP is an important step toward tipping the balance of IOP and perfusion pressure in favor of increased perfusion, and a 30% reduction in IOP has been shown to favorably alter the course of the disease.4 Treatment includes using prostaglandin analogs and carbonic anhydrase inhibitors as first-line agents and adding systemic carbonic anhydrase inhibitors and cholinergic agonists if needed. Currently, some practitioners feel that adrenergic agonists and nonselective beta-blockers may harm NTG patients by possibly decreasing blood flow within the ONH. Certain researchers have advised that these agents be avoided.5,6 Antiserotonin agents such as nastidrofuryl that cause vasodilation and calcium channel antagonists such as nifedipine that block vasospasm may be useful in increasing blood flow to the ONH.1

At this time, the patient was on maximum tolerated medical therapy, and we recommended SLT (Lumenis Inc.,

Figure 2. Two years later, there is superior thinning of the optic nerve in the patient’s right eye (A) and inferior thinning of the optic nerve in her left eye (B). A disc hemorrhage is present in the patient’s right eye.

Figure 3. Seven months later (A), progressive thinning has occurred inferiorly in the optic nerve of the patient’s left eye (B).
Santa Clara, CA). The patient underwent the procedure on her right eye in September and on her left eye in October.

OUTCOME
The patient’s IOP dropped from the low teens in both eyes to 10 mm Hg OD and 9 mm Hg OS. The patient will follow up in 2 months for a determination of her later postoperative course.

DISCUSSION
The clinical diagnosis of NTG entails the observation of glaucomatous optic nerve cupping, progressive visual field defects, and open anterior chamber angles in the absence of elevated IOP.1-4,7 Performing diurnal pressure measurements will rule out pressure spikes. Practitioners should also seek out secondary causes of NTG such as trauma, hypotensive episodes, treatment with corticosteroids, and past ocular inflammation.2

Some patients with NTG progress at a faster rate than others, and efforts are underway to determine risk factors that may indicate the likelihood of progression. According to the NTG Study Group,8 the risk factors of female gender, a history of migraine, and the presence of a disc hemorrhage indicate an increased risk for disease progression. The patient described in this case met all three criteria. It is also important to identify who will benefit most from treatment, and preliminary studies show that an absence of disc hemorrhage at presentation, female gender, a positive family history for glaucoma, a nega-
tive family history for stroke, no patient history of cardiovascular disease, and less disc damage at presentation are all indicators that lowering IOP would be beneficial.

Regarding the pathogenesis of NTG, mechanical factors assume the increased susceptibility of the ONH to IOP such that damage to the ONH occurs at lower IOPs. An increased susceptibility may stem from structural differences in the lamina cribrosa. Also, mechanical factors may include pressure exerted on the optic nerve by ectatic carotid arteries or by masses located in the vicinity of the optic nerve or chiasm. A careful history and examination screening for neurological abnormalities are important for evaluating these conditions. It is also worth considering a CT scan and MRI to rule out an intracranial mass and carotid ectasia, especially for patients younger than 50 years of age.

Vascular factors assume that inadequate perfusion of the ONH causes damage. ONH perfusion depends on ocular perfusion pressure and vascular resistance, and a small rise in IOP in an eye predisposed by increased vascular resistance or decreased ocular perfusion pressure may cause ONH damage. Investigators have hypothesized that vasospasm may contribute to increased vascular resistance and result in glaucomatous damage to the ONH in vasospastic disorders that have been related to NTG such as Raynaud’s phenomenon and migraine. Although researchers have also proposed a vascular insufficiency such as that found in carotid disease as a mechanism for decreased ocular perfusion pressure, various studies have shown different results, and the link is unclear. Microvascular disease is a more likely culprit than macrovascular disease in the pathogenesis of NTG, and it may be more likely that systemic microvascular disease is related to NTG.

Smoking has been examined for its effect on vascular factors that may contribute to inadequate ONH perfusion. Nicotine causes widespread circulatory changes, including vasospastic effects on peripheral small vessels such as the ophthalmic artery that would, in turn, cause increased vascular resistance and decreased ONH perfusion pressure. The patient in this case was a heavy smoker, and

Figure 6. OCT imaging reveals superior and inferior thinning in the optic nerve of the patient’s right eye and superior, inferior, and nasal thinning in the optic nerve of her left eye.
perhaps the local vasospastic response that nicotine induces contributed to the advanced nature of her disease despite our best efforts.16,17

In order to evaluate a patient for vascular factors that may contribute to the development of NTG, the history and examination should screen for microvascular abnormalities such as decreased digital capillary perfusion, a history of myocardial infarction or transient ischemic attacks, and evidence of hyperlipidemia and anemia. Laboratory studies should include CBC, ESR, and lipids to rule out anemia, giant cell arteritis, hyperviscosity, and hyperlipidemia.1

The role of neuroprotection in the treatment of glaucoma is currently under debate. Recent animal studies have shown that glaucomatous retinal ganglion cell death is apoptotic rather than necrotic in nature. The timing of apoptosis depends on the delicate balance between pro-apoptotic and anti-apoptotic signals, and investigators theorize that the role of neuroprotective agents is to tip the balance in favor of anti-apoptotic signaling and cell survival.5 It would follow, then, that preventing apoptosis would avert progression of glaucomatous ONH damage.

Brimonidine is a selective alpha-2 adrenergic agonist shown in rat models to have a direct neuroprotective effect on retinal ganglion cells. Although the exact mechanism is unknown, theoretically, alpha-2 adrenergic receptor stimulation may inhibit pro-apoptotic mitochondrial signaling as well as activate anti-apoptotic signaling pathways.5,6,18

Memantine is another neuroprotective agent recently shown to be useful in the treatment of glaucoma.19,20 This NMDA-type, glutaminergic open-channel blocker decreases the activation of glutaminergic channels. Glutamate is an excitatory neurotransmitter in the central nervous system, and research has shown that glutaminergic excitotoxicity causes neuronal injury in both in vitro and in vivo models of glaucoma.18,20 Increased glutamine levels in the vitreous of glaucoma patients may be a factor in glaucomatous injury to retinal ganglion cells, and systemic treatment with memantine was associated with a reduction in the glaucoma-induced loss of retinal ganglion cells.  

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