NORMAL-TENSION GLAUCOMA: DIAGNOSIS AND TREATMENT

The second in a two-part series on this multifactorial disease subtype.

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Glaucoma is a chronic optic neuropathy characterized by functional visual field deficits and changes to the optic nerve. Although originally thought to be a disease of increased IOP that, if untreated, caused blindness,[1] glaucoma is now recognized as only partly related to IOP. Von Graefe first theorized in 1857 that glaucoma could arise in the context of normal IOP (a condition he called *amaurosis without excavation*).[2] Schnabel verified the theory in 1908,[3] but the concept of normal-tension glaucoma (NTG) did not become widely accepted until the 1980s.[4]

The early diagnosis of NTG is critical because visual field defects are often more significant and located closer to the central visual field than with other types of glaucoma.[5] Prompt diagnosis, however, can be difficult owing to the unreliability of tension-based screening methods in these eyes. Because progressive optic neuropathy can occur at so-called normal IOPs, IOP is not always considered in the definition of glaucoma,[6] further complicating the diagnosis of NTG and perpetuating the search for other mechanisms thought to play a role in its pathophysiology.

Part 1 of this two-part series discussed the prevalence and pathogenesis of NTG (scan the QR code to read now). This article focuses on the diagnosis and treatment of this multifactorial disease subtype.

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DIAGNOSIS AND EVALUATION

Taking a complete medical history and review of systems is the first step in the diagnostic assessment for NTG.[7] The information obtained may point the clinician to the possibility of nonglaucomatous etiologies of optic neuropathy, including central nervous system (CNS) disease or ophthalmic trauma.[7] Often, patients with NTG have a history of migraine headaches, systemic hypotension, cold extremities, or other indications of vascular dysregulation.[7]

Patients being evaluated for NTG should undergo a comprehensive eye examination (including gonioscopy) to investigate possible secondary causes of glaucoma.[7] A single IOP measurement alone may not distinguish between high-tension and normal-tension glaucoma; thus, a diurnal curve can aid in detecting episodes of high IOP outside the clinic.[7] If distinctive findings such as an acquired pit of the optic nerve or optic disc hemorrhages with corresponding visual field defects are present, then CNS imaging or a neuro-ophthalmic consultation is typically not needed.[7] However, as with high-tension glaucoma, if asymmetric disease or visual field defects indicative of a compressive CNS lesion or other nonglaucomatous pathology are present, then further workup may be appropriate.[7]

A complete systemic assessment for possible concurrent diseases, including Raynaud phenomenon and obstructive sleep apnea, is frequently helpful in cases of worsening disease despite IOP-lowering treatment.[7] In some cases, the diagnosis of NTG may lead to the discovery of other systemic conditions.[7] Because IOP-independent risk factors are known to affect the disease process of NTG, coordinating with the patient's internist on further evaluations such as sleep studies and 24-hour ambulatory blood pressure monitoring may be helpful.[7] Nonocular systemic diseases are believed to contribute to worsening NTG; therefore, treatment of possible IOP-independent factors, including systemic hypertension to lessen nocturnal hypotension, can reduce NTG progression.[7] If the disease continues to progress rapidly despite treatment of both IOP and IOP-independent risk factors, the diagnosis of NTG should be reassessed and a workup for nonglaucomatous causes of vision loss pursued.[7]

TREATMENT

Pharmacologic. IOP is still the only confirmed modifiable risk factor for glaucoma treatment.[7] The Collaborative Normal-Tension Glaucoma Study (CNTGS) confirmed the importance of IOP reduction even for statistically normal IOPs[8,9]; a 30% decrease in IOP reduced the long-term risk of disease worsening from 35% to 12%.[8,9] Notably, topical beta blockers

were not used in this study, and more than 50% of patients reached their target IOP without requiring surgery or laser trabeculoplasty.[8-10] CNTGS also confirmed a faster rate of glaucomatous progression in women and in patients with disc hemorrhages or migraine headaches.[10] A higher occurrence of cataract surgery was noted in the treatment group than in the control group.[10] Additionally, nearly 50% of untreated patients did not experience disease progression over 5 to 7 years, suggesting that the benefit of IOP lowering among patients with NTG is not uniform.[11]

Several studies have compared different drug therapies as monotherapy for NTG. The Low-Pressure Glaucoma Treatment Study (LOGTS) was a prospective, randomized clinical trial that compared the use of timolol with brimonidine as monotherapy for NTG.[12] As in the CNTGS, the LOGTS study population had a high proportion of women and patients with optic disc hemorrhages.[12] An average follow-up period of about 30 months showed that patients treated with timolol were more likely to experience visual field worsening than those treated with brimonidine (39.2% vs 9.1); the IOP-lowering effect of both drugs, however, was similar.[13] These findings suggest a possible neuroprotective effect of brimonidine or a neurodestructive effect of timolol when used as monotherapy for NTG. Notably, the study showed a high rate of brimonidine intolerance, with 28.3% of patients discontinuing the medication owing to drug-related adverse events.[13]

Prostaglandin analogues (PGAs) are highly efficacious for IOP lowering and have been shown to control IOP throughout a 24-hour day,[14] making them the gold standard for the medical treatment of glaucoma.[14] Before PGAs, topical beta blockers were considered the first-line IOP-lowering treatment for glaucoma,[7] but these agents may cause systemic side effects, including nocturnal hypotension, that may contribute to NTG progression.[7] As noted previously, LOGTS showed that beta blocker treatment may be harmful in patients with low-tension glaucoma.[13] Hayreh et al also concluded that topical beta blocker use may be an independent risk factor for visual field worsening by contributing to nocturnal arterial hypotension in patients with NTG.[15]

Alpha agonists, especially brimonidine, have demonstrated a neuroprotective effect in animal models of retinal and optic nerve damage.[16] This class of medication reduces IOP mainly by decreasing aqueous production as opposed to augmenting aqueous outflow.[7] Because aqueous production is typically reduced during sleep,[17] the general consensus is that aqueous suppressants have minimal influence on nocturnal IOP.[7] However, Liu et al reported that topical carbonic anhydrase inhibitors, which also decrease the production of aqueous humor, may provide superior diurnal IOP control compared to timolol; of note, these findings have yet to be replicated.[18] The importance of nocturnal IOP lowering is still unclear because data to explain its clinical importance in glaucoma are limited.

Latanoprostene bunod 0.024% (Vyzulta, Bausch + Lomb) is a nitric oxide (NO)–donating PGA with a dual mechanism of action. The drug is dosed once daily to decrease IOP in patients with open-angle glaucoma (OAG) and ocular hypertension.[19-22] The two active metabolites in latanoprostene bunod allow it to affect two pathways.[20-22] First, latanoprost decreases IOP through extracellular matrix remodeling, thus augmenting aqueous humor drainage through the unconventional uveoscleral pathway.[23-25] Second, NO acts on Schlemm canal and the trabecular meshwork to lower IOP by augmenting aqueous humor drainage through the conventional pathway.[23,26-30]

The open-label, single-arm, multicenter JUPITER study was conducted in Japan to investigate the effects of latanoprostene bunod 0.024% dosed once every evening for 52 weeks in 130 patients diagnosed with ocular hypertension or OAG (including pigmentary, pseudoexfoliative, and NTG subtypes).[31] Mean (standard deviation [SD]) baseline IOP (measured at 10 hours) in study eyes was 19.6 (2.9) mm Hg (range, 15.0–30.0 mm Hg).[31] Most (74.6%) baseline IOPs were between 15 and 21 mm Hg, which is unsurprising because of the prevalence of NTG in Japanese populations.[31,32] Mean IOP was significantly reduced from baseline by 22.0% (mean [SD], 15.3 [3.0] mm Hg at week 4; with an even larger reduction noted at all subsequent visits (all time points, $P < .001$).[31] At week 52, the mean IOP was 14.4 (2.7) mm Hg, representing a 26.3% decrease from baseline.[31] The most frequently seen adverse effects in study eyes were conjunctival hyperemia (17.7%), eyelash growth (16.2%), eye irritation (11.5%), and eye pain (10%)[31]; all adverse effects were mild or moderate, and no patient stopped their medication as a result.[31]

A preliminary study of omidenepag isopropyl, a selective prostaglandin EP2 receptor agonist, in patients with NTG had promising preliminary results. The mean IOP (±1 SD) decreased from 15.7 ±2.6 mm Hg at baseline to 13.6 ±2.4 mm Hg at 4 months.[33] However, 7.4% of patients experienced adverse drug reactions, such as eye pain and conjunctival hyperemia.[33] Because of the risk of cystoid macular edema, omidenepag isopropyl has not been approved for use in pseudophakic patients.[34] Additional studies are needed to elucidate the drug's role in treating NTG.[34]

Rho kinase inhibitors are a newer class of medication that has demonstrated successful IOP reduction in NTG or as add-on treatment in NTG eyes with a baseline IOP above target.[35,36] Medications in this class include ripasudil (Glanatec 0.4%; Kowa) and netarsudil (Rhopressa 0.02%; Alcon).[35,36]

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Rho kinase inhibition augments the NO pathway in the trabecular meshwork endothelium, thereby improving trabecular outflow and possibly increasing blood flow to the optic nerve head.[34] Preliminary studies of ripasudil also showed increased parapapillary vessel density on OCT angiography.[37]

Laser therapy. Because patients with NTG typically have baseline IOPs in the statistically normal range, it is challenging to lower IOP to the single digits with medical therapy alone. Nonmedical treatments for addressing NTG and "high-pressure" OAG are the same. Laser trabeculoplasty has been shown to achieve greater diurnal control than some frequently utilized ocular hypotensive medications.[38,39] However, the Early Manifest Glaucoma Trial (EMGT) showed that treatment with the combination of argon laser trabeculoplasty and the beta blocker betaxolol did not lower IOP significantly in NTG eyes with a baseline IOP of 15 mm Hg or less, indicating that laser trabeculoplasty may be minimally effective in patients with NTG.[40]

Micropulse laser cyclophotocoagulation and selective laser trabeculoplasty have also been investigated for NTG. In one study, selective laser trabeculoplasty achieved a 27% reduction in number of medications and a 15% reduction in mean IOP in eyes with NTG.[41] In a study evaluating the effectiveness and safety of micropulse laser cyclophotocoagulation, a positive, although more limited, response (average 20.1% IOP reduction from baseline) was seen in patients with NTG and a baseline IOP of 21 mm Hg or less.[42] No patient experienced phthisis bulbi, sympathetic ophthalmia, persistent inflammation, or hypotony in this study.[42]

Surgery. Filtering surgery is the next therapeutic option when IOP is not adequately controlled with medical treatment or laser trabeculoplasty. Because the target IOP is frequently lower in NTG than in primary OAG, patients with NTG are at higher risk for ocular hypotony, and thus hypotony maculopathy, postoperatively.[43] Still, trabeculectomy is the most successful treatment option for attaining low IOPs.[7] Trabeculectomy has also been shown to reduce diurnal and nocturnal IOP fluctuations, even during postural movements.[44,45] Song and Caprioli noted that, because IOP fluctuates minimally in the setting of a well-functioning bleb and is independent of patient compliance, disease worsening in NTG was frequently reduced after trabeculectomy even if comparable IOP reductions were attained previously with medical treatment.[7]

The popularity of aqueous shunts has increased, partly owing to the Tube Versus Trabeculectomy (TVT) study.[46-48] This study compared the outcomes and complication rates of tube shunt surgery using a Baerveldt-350 implant (Johnson & Johnson Vision) versus trabeculectomy in eyes with a history of cataract and glaucoma surgery.[47,48] Five years of follow-up showed that tube shunt surgery was correlated with a lower failure rate and fewer complications than trabeculectomy in eyes with a history of surgery.[47,48] Notably, the TVT study did not show the superiority of tube shunts over trabeculectomy as initial glaucoma surgery.[47,48]

Tran et al compared the Ahmed Glaucoma Valve (New World Medical) with trabeculectomy using stricter criteria for success than the TVT (IOP < 18 mm Hg and an IOP reduction > 20% from baseline). The investigators noted that trabeculectomy had a significantly higher 5-year cumulative probability of success than the implants when greater IOP reduction was needed.[49] Because trabeculectomy attains a lower postoperative IOP than glaucoma drainage devices, the former is likely a more appropriate surgery in NTG eyes. Although not statistically significant, the TVT study also reported decreased mean IOP in the trabeculectomy group (12.6 ±5.9 mm Hg) compared to the tube shunt group (14.4 ±6.9 mm Hg) after 5 years of follow-up.[49]

Nonpenetrating glaucoma surgery, or MIGS, offers the theoretical advantage of decreasing the risk of complications associated with more aggressive surgeries to lower IOP.[7] During nonpenetrating deep sclerectomy, the internal wall of Schlemm canal is removed without penetrating the anterior chamber.[7] Lachkar et al performed a retrospective analysis and demonstrated that nonpenetrating deep sclerectomy was correlated with an IOP reduction of 33.73 ±20.9% after 6 years, with minimal complications.[50] Additional studies comparing trabeculectomy with nonpenetrating deep sclerectomy have confirmed these IOP-lowering outcomes with even lower complication rates.[51-53]

In an analysis of the AAO IRIS Registry data on usage patterns of MIGS from 2013 to 2018, the iStent (Glaukos) was the most frequently used MIGS approach in eyes with NTG.[54] In a multicenter study of the iStent inject (Glaukos), Clement et al found that, at 24 months, mean IOP was lowered by 16%, from 16.4 ±4.7 mm Hg preoperatively to

13.7 ±3.1 mm Hg; 77% of eyes had an IOP of 15 mm Hg or less compared to 49% before surgery.[55] The average number of medications was reduced by 67%, from 1.49 ±1.20 preoperatively to 0.49 ±0.95 postoperatively, and the rate of complications was low.[55] Another study showed that the Xen Gel Stent (Allergan) was as or more efficacious in lowering IOP as trabeculectomy and associated with less hypotony[56]; in this study, IOP in patients with NTG decreased from 16.6 ±3.4 to 11.6 ±2.2 mm Hg.[57] Although these less invasive surgical procedures may play an important part in the treatment of NTG and other types of glaucoma in the future, studies with longer follow-up are needed to better evaluate effectiveness and safety.

OTHER TREATMENT OPTIONS

Although IOP lowering is successful in treating NTG, a substantial percentage of patients still experience disease progression. Thus, researchers are investigating IOP-independent, neuroprotective treatment options.

Glutamate is an excitatory neurotransmitter in the retina and CNS.[7] Glutamate excitotoxicity has been linked to retinal ganglion cell death in experimental models of glaucoma.[58,59] The blockage of higher-than-normal levels of glutamate by inhibiting its receptor, N-methyl-D-aspartate, has been suggested as a therapeutic focus for neuroprotection in glaucoma.[60] Memantine is a clinically helpful medication, used mostly in Alzheimer dementia, that functions by hindering flow through the N-methyl-D-aspartate receptor.[61] Several preclinical investigations in animal models of glaucoma have shown memantine to be protective,[62-65] but a randomized, multicenter clinical trial did not demonstrate an equivalent outcome in human glaucoma.[66]

Calcium channel blockers (CCBs) are typically used to treat systemic hypertension and other cardiovascular conditions.[67] These agents impede voltage-gated calcium channels in vascular smooth muscle, causing vasodilation and reducing contractility.[7] Gasser and Flammer explored the role of peripheral vasospasm in NTG and the possible use of CCBs to enhance ocular perfusion.[68-70] Later studies showed that centrally acting CCBs, including nifedipine and nimodipine, enhanced color sensitivity and ocular blood flow in glaucomatous eyes.[71-73] Low-dose nifedipine has been shown to reverse ocular hemodynamic changes caused by ET-1.[74] Nonetheless, reports on functional improvement are mixed.[75-78] Some animal studies have shown IOP lowering with the use of topical CCBs, although the mechanism of action for this effect is unclear.[55,79-81] Topical verapamil, however, has been reported to cause only a mild decrease in IOP in normal human eyes.[82-84] The possible advantages of CCBs have yet to be fully investigated in randomized controlled trials. Further, certain patients are intolerant of the drugs' side effects, especially peripheral edema and related complications.[7] Additionally, peripheral vasodilation, caused by CCBs, may cause systemic hypotension and lower diastolic ocular perfusion pressure to the optic nerve, which may induce further damage in NTG.[7]

In recent years, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, known as *statins*, have been recognized as a possible treatment for glaucoma. Because statins not only lower lipids but are also antiapoptic and neuroprotective, their extended use may decrease the risk of glaucoma.[85-87] However, studies have shown mixed results on statins' protective effect; thus, an interventional prospective study is needed to clarify the possible benefit of statins for treating NTG and other types of glaucoma.[87-89]

Nutritional supplements and phytochemicals are being investigated as additional treatments for glaucoma. Ginkgo biloba, a species of tree native to Korea, Japan, and China, is one example.[90] Ginkgo extracts, made mostly of terpenoids and flavonoids, have been used therapeutically, especially for their supposed nootropic effects on memory and cognition.[91] These effects are thought to be due to ginkgo biloba's vasorelaxant abilities.[91] Additional investigations have shown that ginkgo extracts may possess antioxidative capabilities.[92-94]

Park et al found increased peripapillary blood flow in patients with NTG who ingested ginkgo biloba extract compared with those who did not ingest the extract.[94] Harris et al demonstrated that antioxidant supplementation, when compared with placebo, reduced vascular resistance in central retinal and nasal short posterior ciliary arteries and elevated blood flow velocity within the superior and inferior temporal retinal capillaries.[95] The ginkgo extract EGb761 has been shown to be neuroprotective in animal models of ischemic CNS injury,[96,97] and human studies have shown better visual field indices in correlation with the ingestion of ginkgo extracts in patients with NTG.[98-100] Patients, however, should be warned of the risk of seizure disorders and bleeding.[101]

Resveratrol is a polyphenol frequently present in berries, nuts, and the skin of red grapes.[102,103] First isolated in 1940 from the root of *Veratrum grandiflorum*,[104] resveratrol has potential antioxidative and antiinflammatory properties that may be beneficial in age-related conditions, including glaucoma.[102,103] One mechanism by which resveratrol is considered to be vasoprotective is by impeding ET-1 synthesis.[105] Resveratrol has also been shown to inhibit trabecular meshwork damage in the presence of chronic oxidative stress[106] and to restore protein levels that are diminished in glaucoma and play a role in mitochondrial biogenesis.[107] The polyphenol not only changes the number of mitochondria but also improves their quality.[107]

Although preliminary data are encouraging, additional human studies are needed to confirm the results and increase understanding of these therapies.

CONCLUSION

NTG is a multifactorial subtype of OAG. Associated factors include but are not limited to oxidative stress, ocular perfusion, the effect of a difference between CSF and translaminar cribrosa pressure, and IOP.[7,34,108] Several factors may play a role in the pathogenesis of NTG. IOP-independent risk factors such as ocular blood flow, vasospasm, and endothelial dysfunction are likely key contributors.[7,34,108]

Although patients with NTG display statistically normal IOPs, IOP lowering is the most established treatment. Medications are still first-line treatment options for this condition. When medications are no longer sufficiently controlling IOP in the background of visual field worsening and progressive optic nerve injury, glaucoma filtering surgery is typically the next option. It is to be hoped that both IOP and IOP-independent risk factors will be addressed by future treatment options. Additional research is needed to craft clinically successful IOP-independent neuroprotective treatment options for NTG and to further understand its complex pathophysiology. ■

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