NORMAL-TENSION GLAUCOMA: PATHOGENESIS

The first 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. Glaucoma was originally understood to be exclusively a disease of increased IOP that, if untreated, caused blindness,[1] but it is now recognized that glaucoma can occur in the context of normal IOP.[2] Von Graefe first theorized that glaucoma could arise in the context of normal IOP in 1857, and he called this condition *amaurosis without excavation*.[3] Schnabel verified the theory in 1908,[4] but the concept of normal-tension glaucoma (NTG) did not become widely accepted until the 1980s.[5]

Studies have since demonstrated the prevalence of NTG. In the Baltimore Eye Survey, half of the participants with primary open-angle glaucoma (POAG) had an IOP of less than 21 mm Hg at the time of diagnosis; 20% of this subset had an IOP of less than 21 mm Hg on each of their initial three visits.[6,7] Several population-based studies have validated that NTG is more prevalent than once believed. The mean percentage of NTG in all patients diagnosed with a glaucomatous visual field defect is between 30% and 40%.[6,8,9] The prevalence of NTG has been reported to be 92.3% in Japan,[10] 84.6% in Singapore,[11] 83.58% in Northern China,[12] 82% in South India,[13] 79.3% in Southern China,[14] 77% in South Korea,[15] 57.1% in South Africa,[16] 46.9% in Iran,[17] 38.9% in Netherlands,[9] 31.7% in the United States,[18] 31.0% in Iceland,[19] and 30.0% in Italy.[20] Research has also shown racial and ethnic disparities in the prevalence of NTG, with a higher proportion of Asian individuals affected than patients of African descent, followed by Caucasian patients.[21] The reasons for these differences are unknown.[9-19]

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.[23] Prompt diagnosis, however, can be difficult owing to the unreliability of tension-based screening methods in these eyes.[2] Because progressive optic neuropathy can occur at so-called normal IOPs, IOP is not always considered in the definition of glaucoma,[23] further complicating the diagnosis of NTG and perpetuating the search for other mechanisms thought to play a role in its pathophysiology.

POAG VERSUS NTG

NTG has been defined as glaucoma with an IOP of less than 21 mm Hg.[24] It has been theorized that POAG and NTG are on opposite sides of the spectrum of open-angle glaucomas.[24] IOP is theorized to be the main risk factor in POAG, whereas IOP-independent risk factors are believed to play a crucial role in NTG.[24] Clinically, it is imperative to differentiate pure POAG and NTG at each end of this continuum from *mixed* disease in the middle.[2] IOP reduction is the mainstay of treatment in POAG,[2] but reducing IOP alone may not be sufficient for treatment of NTG or mixed disease.[2]

Beyond IOP, nuanced clinical distinctions exist between POAG and NTG. In NTG eyes, the optic disc often presents with a narrower neuroretinal rim, especially inferiorly and inferotemporally.[25] Beta zone peripapillary atrophy and disc hemorrhages are more commonly noted in NTG, and the presence of disc hemorrhages indicates a worse prognosis in NTG.[26,27] Peripapillary crescents and haloes are present more frequently at the disc margin and appear to be regions of deficient retinal pigment epithelium.[28]

Localized cupping is also sometimes noted at the optic disc margin.[28] These focal areas of cupping may be acquired pits of the optic nerve (APON), which are more common in NTG.[29,30] They are frequently seen in the inferior optic disc and are linked to a higher incidence of disc hemorrhages and an elevated risk of worsening glaucoma.[30,31] The presence of APON is also correlated with visual field deficits that often arise near fixation, similar to paracentral scotomas seen in NTG (Figures 1 and 2).[30] Studies have shown that visual field defects in NTG are frequently more substantial, more focal, and more central than visual field deficits in POAG with elevated IOP.[32,33]

Although dissimilarities between POAG and NTG are often noted,

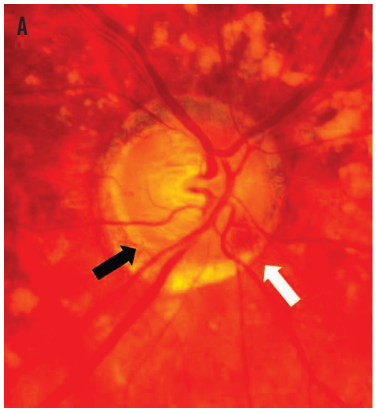

Figure 1. Right optic nerve. The black arrow indicates an inferotemporal APON (A). The inferonasal area (white arrow) also shows a disc hemorrhage. Standard automated perimetry demonstrates a superior paracentral arcuate defect and a corresponding inferior paracentral arcuate defect due to superior rim narrowing (B). Reprinted with permission from Brian Song, MD; Joseph Caprioli, MD, and Medknow Publications.[23]

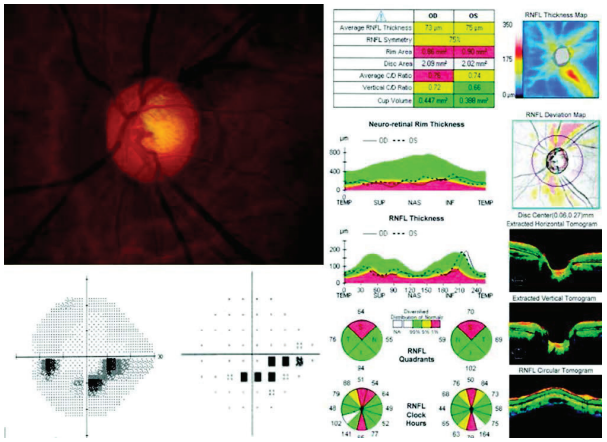

Figure 2. Left optic nerve with a superotemporal APON. OCT scan of the retinal nerve fiber layer shows corresponding thinning. The visual field reveals a corresponding inferior paracentral arcuate defect.

clinical interpretation of these conditions is inconsistent; thus, there is likely some commonality in the fundamental pathogenesis of glaucomatous optic neuropathy between these two types of glaucoma.[24]

PATHOGENESIS

Ocular perfusion and hypotension. Systemic factors may play a role in the pathogenesis of NTG. The Collaborative Normal Tension Glaucoma Study (CNTGS) showed that, although IOP lowering slowed glaucomatous progression, the 5-year survival rate was 40% in the control arm and 80% in the treated arm.[34] This suggests that either a 30% reduction from baseline IOP was inadequate for some patients or causes other than IOP played a role in the pathophysiology of the disease.

In 1858, Jaeger suggested that injury to the optic nerve head (ONH) was associated with a change in vascular perfusion.[35] In 1959, Harrington suggested that decreased blood flow makes the optic nerve vulnerable to glaucomatous damage, even when IOP values are statistically normal.[36] In 1962, Haas noted that vascular insufficiency may increase the optic nerve's susceptibility to IOP-related damage.[37] In 1968, Johnson and Drance introduced the idea of ocular perfusion pressure (OPP) and suggested that systemic hypotension may play a significant role in NTG.[38] In the late 1990s, decreased peripapillary retinal blood flow was also noted in NTG.[39]

Several epidemiologic studies have documented the importance of OPP. In the Baltimore Eye Study,[40] a diastolic OPP greater than 50 mm Hg (signifying high perfusion) was associated with a race and age-adjusted risk of OAG that was six times lower than a diastolic OPP lower than 30 mm Hg.[40] The study authors concluded that OAG correlated to changes in ocular blood flow and damage to autoregulation.[40] In the Barbados Eye Study,[41] the 9-year relative risk of incident OAG with a low mean OPP was 2.6. The Egna-Neumarkt Study[42] showed a higher prevalence of OAG with decreased diastolic OPP. The Proyecto Ver Study showed a four times higher risk of OAG in patients with diastolic OPPs lower than 50 mm Hg compared with diastolic OPPs lower than 80 mm Hg.[43] The Rotterdam Study also showed that a low diastolic OPP was correlated with OAG in patients treated for systemic hypertension.[44] In the Singapore Malay Eye Study, OAG was more frequently seen in patients with a mean OPP in the lowest quartile versus the highest quartile (odds ratio, 1.73).[45] The Early Manifest Glaucoma Trial (EMGT) demonstrated that a low systolic OPP was a prognosticator of worsening glaucoma, with a hazard ratio of 1.42.[46] The investigators determined that a vascular etiology may be responsible for glaucomatous progression.[46] All of these studies suggest that overtreating systemic hypertension may cause low blood pressure (BP), low OPP, and glaucomatous progression.

Hypotension, especially nocturnal low BP, has been seen more frequently in NTG.[47,48] Multiple studies have reported hypotension and circadian changes in the mean OPP as key risk factors for visual field defect progression in NTG.[49-52] Hypotension causes low OPP and reduces ocular blood flow; optic nerve fibers thus suffer from a diminished blood supply. This is of particular importance for nocturnal BP "dippers."[53]

Autoregulation. Blood flow autoregulation is the innate capability of the vasculature to maintain steady blood flow over a wide range of BPs while meeting the metabolic needs of a tissue.[21] Autoregulation is known in many vascular arenas, including the eye,[54] heart,[55] kidney,[56] brain,[57] gut,[58] and skeletal muscle.[59] Vascular dysregulation is a tissue's inability to provide a continuous blood supply with fluctuations in perfusion pressure.[53]

The ONH is served by a complicated vascular mechanism.[45,60,61] Autoregulation of the ONH may be damaged by various pathologies.[62] A study of the autoregulation of retrobulbar hemodynamics showed unchanged flow velocities in the

short posterior ciliary arteries of healthy patients despite changes in posture.[63] In contrast, an inadequate compensatory reaction to postural change has been found in patients with NTG and POAG.[63] Because a disruption of autoregulation is a risk factor for worsening glaucoma,[64-66] destruction of the optic nerve in NTG is believed to be due to vascular dysregulation and recurring reperfusion damage to the optic nerve.[67] Moreover, the greater number of disc hemorrhages in these patients suggests a vascular cause of the optic nerve injury seen.[68] Studies have also shown that patients with glaucoma have decreased end-diastolic velocities and increased resistivity indices in the central retinal artery, central retinal vein, ophthalmic artery, and lateral and medial short posterior ciliary arteries.[69]

The vascular endothelium is a crucial component of ocular blood flow autoregulation. By creating a layer of cells between blood and the vessel wall, dysfunction in the vascular endothelium may lead to a lack of blood flow autoregulation and ensuing ischemia to the ONH.[70] Of note, the vascular endothelium is critical to hemostasis, angiogenesis, and inflammatory reactions.[70]

Endothelial pathologic changes may be instigated by oxidative stress, which causes deviations in the cellular concentration of mediators created by endothelial cells.[21] Persistent endothelial damage can result from smoking, heart and renal failure, systemic hypertension, hypercholesterolemia,[71] and elevated plasma homocysteine.[72] Endothelial damage is predictive of cardiovascular disease occurrences and long-standing atherosclerotic disease worsening. Endothelin-1 (ET-1) is an endothelium-derived vasoregulatory molecule that serves as an endogenous vasoconstrictor, most commonly on small vessels.[73-75] It is created and deposited from the ciliary processes in the eye and is thought to play a role in the control of ocular blood flow.[73,76] Preclinical studies have shown that intravitreal injections of ET-1 can reduce perfusion of the ONH and cause apoptosis of retinal ganglion cells (RGCs).[77-79] Unsurprisingly, a disproportion in ET-1 (which facilitates vasoconstriction) and nitric oxide (which facilitates vasodilation) is seen in glaucoma and contributes to endothelial pathologic changes. Some studies have connected NTG and higher ET-1 with subclinical inflammation and heart rate changes.[80,81]

The decreased availability of nitric oxide reduces blood flow to the ONH.[82,83] Vasospasm is essentially an amplified vascular reaction to factors such as stress and temperature.[84,85] Migraine and Raynaud phenomenon are two vasospastic conditions that are known risk factors for NTG.[86] The CNTGS found that migraine is a risk factor for worsening disease.[87] Obstructive sleep apnea is also more prevalent in NTG.[88-90] ET-1 may play a role in vasospasm because basal plasma ET-1 is increased in NTG, with atypical plasma ET-1 concentrations seen in response to fluctuations in temperature[91] and posture.[92]

The inflammatory cytokine tumor necrosis factor-α is highly stimulated by ischemic and pressure-overloaded glial cells, which causes RGC death.[93-95] In contrast, decreased tumor necrosis factor-α may have a neuroprotective effect.[93-95] This implies that an inflammatory, subclinical etiology may play a role in glaucoma and is likely why a link between autoimmune disease and NTG has been proposed. Cartwright et al showed that 30% of patients with NTG and 8% of control patients with ocular hypertension were diagnosed with one or more immune-related diseases.[96] A higher incidence of paraproteinemia and autoantibodies has also been shown in NTG.[97-99] An investigation of autoantibodies noted in the sera of patients with glaucoma discovered IgG antibody patterns against retinal antigens in patients with POAG and NTG.[100,101] A subsequent study identified these antigen bands as vimentin, heat shock protein 70, and $\alpha\beta$-crystallin.[101]

The role of retinal venous pressure (RVP) in glaucoma has also been studied. RVP is the IOP at which the vein at or near the ONH begins to pulsate,[102] and it is increased in patients with glaucoma.[102-104] One possible theory for the role of ET-1 is that, when increased, it diffuses from fenestrated capillaries of the choroid into the ONH, circumventing the blood-retinal barrier, increasing the local concentration of ET-1, and leading to the constriction of retinal veins and an elevation of RVP.[102,105] Another theory is that increased production from nearby diseased artery or retinal tissue elevates the local concentration of ET-1.[102] Perhaps elevated RVP leads to lower perfusion pressure and increases the possibility of hypoxia surrounding the ONH.[102] A study from Switzerland assessed the effect of low-dose nifedipine on RVP in patients with POAG; although there was a statistically significant decrease in RVP before and after treatment (mean decrease of 12.5 mm Hg [SD, 12.5]; $P < .001$), there were no significant differences in IOP.[106] Studies of the importance of RVP in glaucoma and the effectiveness of treatment are warranted.

In 2012, Mroczkowska et al showed subclinical vascular aberrations at the micro- and macrovascular level in patients who were newly diagnosed with NTG.[107] The higher prevalence of systemic diseases such as obstructive sleep apnea, migraine headaches, and Raynaud phenomenon in individuals with NTG suggests vascular irregularities.[24,87-90,108]

Oxidative stress. Reactive oxygen species (ROS) are created as a result of cellular metabolism.[21] Although they play a key role in cell signaling and regulation, an excessive amount may overwhelm cells' innate antioxidant capacity.[21] This, in turn, may lead to structural damage, including DNA, proteins, and lipids.[21] Oxidative stress can cause RGC death and, subsequently, glaucomatous optic neuropathy.[109] One possible mechanism is for ROS

to cause enzymatic oxidation of particular amino acid residues, thus acting as a second messenger and/or modulating protein function.[109] Another study showed that ROS activate the antigen-presenting capability of glial cells and act as costimulatory molecules during antigen presentation; this may ignite an immune response during glaucomatous optic nerve damage.[110]

Neurovascular coupling. There is evidence of a link between the ONH vasculature and RGC neuronal activity.[111,112] When activated by light, neurons either transmit a signal to blood vessels or stimulate astrocytes to exude vasoactive chemicals onto vessels to augment the flow of blood; neurotransmitter signaling, including glutamate, plays a role in both situations.[113] Studies have suggested that hypoxia/perfusion variability may affect the ONH astrocytes[114] and the mitochondria of RGC axons.[115] This may lead to RGC autophagy[116] and/or apoptosis.[115] Alternatively, hypoxia could destroy astrocyte-astrocyte gap junctions, altering the homeostasis of RGC axons, damaging the autoregulatory abilities of ONH blood vessels, and leaving the ONH vulnerable to destruction.[114]

Cerebrospinal fluid pressure and translaminar cribrosa pressure difference. Recent studies have indicated that local tissue and biomechanical factors may influence the ONH's vulnerability to pressure. Glaucomatous damage occurs at the lamina cribrosa,[117] which is the boundary between the retrolaminar compartment (optic nerve interstitial pressure and retrobulbar cerebrospinal fluid pressure [CSFP]) and the intravitreal compartment (IOP).[118-120] The translaminar cribrosa pressure difference (TLCPD) is the difference between IOP and retrobulbar CSFP. It is not the IOP but the TLCPD that acts on the lamina cribrosa.[21] A low retrobulbar CSFP, as opposed to elevated IOP, can increase the TLCPD in patients with NTG.[119] A link between elevated CSFP and lower BP, younger age, and a higher body mass index (BMI) has also been found.[120] This may explain the high prevalence of NTG in Japan, where patients with NTG were older and often had lower BP and a lower BMI.[10] It may also explain the comparatively lower reported prevalence of NTG in the United States, where patients with NTG had higher BP and a higher BMI.[18] An increased BMI may even be protective against glaucoma.[121-124]

The Beijing Eye Study showed a stronger correlation between TLCPD and OAG (but not angle-closure glaucoma) than between IOP and OAG; a correlation was also present between TLCPD and the extent of glaucomatous optic nerve damage.[125] This may support the role of TLCPD in NTG. The Korean National Health and Nutrition Examination Survey showed that TLCPD was linked with the prevalence of NTG in patients whose IOP was in the high teens but not in those whose IOP was in the low teens; on the other hand, systemic hypertension was more significantly linked with NTG in patients whose IOP was in the high teens.[126] This suggests different root causes for NTG with IOPs in the low versus high teens.[126] Leung et al performed a prospective cohort study of 470 eyes of 470 patients from a Hong Kong database; the investigators defined low-teens and high-teens NTG as a maximum untreated office IOP of 15 mm Hg or less and greater than 15 mm Hg, respectively, at all serial visits. Upon comparing the two groups according to these definitions, the investigators found that vascular risk factors were more common in the low-teens group.[127]

Further research into the role of TLCPD in NTG is warranted.[21] The development of a noninvasive measurement of retrobulbar CSFP (instead of lumbar puncture) would allow TLCPD to be applied more broadly.[21] In the past, a variety of methods were used, including Tympanic membrane reflectivity and ophthalmodynamometric venous pulsation pressure measurement as surrogates.[21] Recently, an MRI-assisted measurement of the orbital subarachnoid space width was evaluated as a surrogate for CSFP; it proved to be helpful if the BMI and mean arterial BP were included in the measurement as well.[128]

For some reason, NTG patients have a lower CSFP compared to the normal population.[129,130] One reason may be that the pressure gradient across the lamina cribrosa may change exclusively of IOP, as shown in animal studies.[131,132] Theoretically, decreased CSFP may lead to higher translaminar pressure, which may then worsen glaucomatous optic neuropathy.[133]

Silent cerebral infarcts. The optic nerve is essentially a continuation of the central nervous system (CNS), where RGCs play a specific role.[21] A silent cerebral infarct (SCI) is an infarct of the brain due to vascular obstruction coincidentally seen on MRI or computed tomography without the presence of clinically evident focal neurologic signs.[21] An SCI is an independent risk factor for a potential stroke.[134] MRI brain studies have shown vascular damage in patients with NTG.[135] This finding has been confirmed by studies showing that ischemic insults are visible with MRI in 34% of patients with NTG.[136,137] This link is plausible if the optic nerve is a part of the CNS because both are affected by the same risk factors.

Theoretically, vascular damage to the CNS can lead to the same damage to the optic nerve, decreasing perfusion and increasing the risk of NTG.[21] Leung et al conducted a prospective cohort study of this relationship.[138] SCIs were noted in 29.6% of patients with NTG and visual field worsening versus 15.3% of patients with NTG and stable visual fields ($P = .004$) after 3 years of follow-up.[139] Kaplan-Meier survival analysis showed progression in 65.6% of SCI-positive patients and 45.9% of SCI-negative patients ($P = .003$).[138] Cox

proportional hazards regression analysis showed the presence of a disc hemorrhage (hazard ratio [HR] 2.28; 95% confidence interval [CI], 1.54–3.37; $P < .001$), central corneal thickness (per 30 µm of thinning; HR 1.35; 95% CI, 1.16–1.75; $P < .001$), systemic hypertension (HR 1.48; 95% CI, 1.04–2.10; $P = .029$), and SCI (HR 1.61; 95% CI, 1.09–2.36); $P = .016$) were correlated with visual field worsening.[138]

Subsequent studies have shown that MRI evidence of cerebral small vessel disease (SVD) is linked with POAG and with the level of damage to the visual field and cup-to-disc ratio.[139,140] Currently, SCI is believed to be on the continuum of SVD.[141] First coined in 1873, the term SVD is defined as any pathology that insults brain capillaries, venules, arterioles, and small end arteries and decreases or hinders perfusion of the affected organ.[141] SVD mainly damages organs that obtain large percentages of cardiac output, including the brain and retina.[141] It mainly affects the vascular endothelium[142] and is primarily driven by systemic hypertension.[143] A well-functioning endothelium regulates vascular penetrability to plasma constituents, decreases leukocyte and platelet accumulation, and controls vascular tone; these are critical for blood flow to meet a tissue's metabolic needs and support blood vessels.[142] Endothelial damage leads to lipohyalinosis and arteriolosclerosis.[21] Research on SVD is ongoing. Additional studies are needed to investigate the effect of SVD treatment on NTG.[21]

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 CSFP and translaminar cribrosa pressure, and IOP.[2,21,53] 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.[2,21,53] Part two of this series will review the diagnosis and treatment of NTG. ■

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