Normal tension glaucoma in Asia: Epidemiology, pathogenesis, diagnosis, and management

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Abstract:
Normal tension glaucoma (NTG) has similar optic neuropathy as primary open-angle glaucoma (POAG), but intraocular pressure (IOP) is within the normal range. Compared with high-pressure POAG, the development of NTG is possibly a consequence of a complex interaction of several ocular and systemic factors. Recent data have shown higher translaminar pressure gradient due to impaired cerebrospinal fluid dynamics may account for the pathogenic mechanism. Insufficient blood supply and vascular dysregulation may also be the cause of the disease. In clinical evaluation, NTG is a diagnosis by excluding other nonglaucomatous optic neuropathies. NTG is characterized by larger and deeper optic-disc cupping, more central visual field defects and a higher incidence of disc hemorrhage compared with POAG. In clinical practice, controlling IOP as low as possible (with medication, laser trabeculoplasty, or surgery) is the key to manage NTG patients. In addition to IOP reduction, the control of systemic risk factors or improving ocular perfusion may be beneficial therapies. NTG is more prevalent in Asia than in the Western countries. Due to increasing old population and underdiagnoses in the clinical settings, NTG became a great challenge for ophthalmologist in Asia. Therefore, the aim of this article is to focus on the epidemiology, to update pathogenesis, diagnosis, and management for NTG.

Keywords: Diagnosis, epidemiology, management, normal tension glaucoma, pathogenesis

Introduction
Normal tension glaucoma (NTG) is a progressive optic neuropathy with an intraocular pressure (IOP) within the normal range (<21 mmHg, i.e., below the statistical upper limit of normal range).¹ The characteristics of structural and functional impairment are similar to primary open-angle glaucoma (POAG). Both glaucoma have normal anterior chamber angles, peripapillary retinal nerve fiber layer (RNFL) thinning, glaucomatous optic neuropathy, and corresponding visual field (VF) defects.² It has been postulated that NTG is a disease within the spectrum of POAG. However, different mechanisms may have been implicated in the pathogenesis of NTG versus high-pressure POAG. The complexity of the pathophysiology included some IOP-independent risk factors.¹ In Asian countries, more than 70% of POAG are NTG.¹ With the elderly population grown in recent years, the NTG population increased correspondingly. The absence of elevated IOP may cause a large majority of such patients undiagnosed and became a great challenge to ophthalmology community. Therefore, we aim to report the epidemiology, to update the pathogenesis, diagnosis and management for NTG.

Epidemiology
In Asia, the prevalence of POAG is about 2.34%³. The proportion of NTG varies depending on different population and methodology. In previous epidemiological
Pathogenesis

The etiology of NTG is multifactorial and still not well understood. The most important ocular factor is IOP. NTG eyes may have demographically different tolerance and/or genetic susceptibility to an IOP within the normal limit. With a lower IOP threshold, structural thinning in myopic eyes might increase vulnerability to glaucomatous damage even within the IOP reference range. Another cause is the IOP-related deformation of the lamina cribrosa (LC). The IOP-related stress and strain may cause damage onto axons, capillaries, and astrocytes within the LC. LC is a thin collagen tissue that contains unmyelinated retinal ganglion cell axons, forming a barrier between intraocular and the orbital subarachnoid space. Alterations in this transmural cribrosa pressure difference (TLPD, calculated as pressure gradient between intracrural pressure and IOP) induce structural changes in the LC. In case of normal IOP and lower intracranial pressure, the TLPD increases accordingly to cause progressive optic neuropathy. The authors also reported a too-low intracranial pressure would stop cerebrospinal fluid (CSF) flowing from the optic nerve subarachnoid space, resulting in CSF compartment syndrome. This phenomenon may reduce the CSF turnover rate and cause a deficient clearance of toxic substances harmful to the optic nerve. Clinical observation had also found a positive correlation between VF loss and the TLPD in glaucoma, and the neuroretinal rim area was negatively correlated with this pressure.

In addition to IOP and intracranial pressure, insufficient blood supply and vascular dysregulation may be associated with NTG pathogenesis as well. Systemic hypotension, particularly nocturnal low blood pressure (BP) and circadian fluctuations could decrease blood supply to the optic nerve. Previous studies showed the duration and magnitude of decrease in nocturnal BP, particularly 10 mmHg lower than daytime BP (over-dipper), were risk factors for VF progression in NTG patients. The mean ocular perfusion pressure (OPP) is calculated as 2/3 (mean arterial pressure – IOP). The reduction of OPP was an important risk factor for deterioration of optic neuropathy and fluctuation of mean OPP also correlated with VF progression. Each 1-mmHg increase in mean OPP fluctuation was associated with a 27% greater chance of progression in NTG patients. Another cause of reduced ocular perfusion is the obstructive sleep apnea/hypopnea syndrome. Repeated upper airway obstruction, transient hypoxia, and diminished cerebral perfusion pressure may result in the reduction of blood flow to the optic nerve. A higher prevalence of NTG was noted in patients with obstructive sleep apnea/hypopnea syndrome, and a negative correlation was found between the disease severity and RNFL thickness. The concept of vascular dysfunction was first proposed by Flammer and Mozaffarieh. Primary vascular dysregulation or Flammer syndrome is characterized by an insufficient or improper adaptation of blood flow for the tissue needs. It is more prevalent in women and Asians, with an altered response to cold or stress, long sleep onset time, reduced feeling of thirst, and BP drop at night. Local vasospasm and impaired autoregulation were suggested to cause glaucomatous injury in NTG patients.

Diagnosis

NTG is a diagnosis by excluding other similar optic nerve diseases. Currently, the standard diagnostic criteria include glaucomatous structural changes in optic nerve head/RNFL and functional changes on VF, which are the same as those established for POAG. To distinguish NTG from POAG and other differential diagnoses, the medical history should be carefully recorded, including the history of eye trauma or surgery, family history of glaucoma, systemic diseases, and medications taken by patients. Ophthalmic examination should consist of best-corrected visual acuity, color test, Goldmann applanation tonometry, gonioscopy, fundus photography, and 24-2 standard automated perimetry. Pachometry for central corneal thickness (CCT) should be performed because a thinner CCT may underestimate a true higher IOP. Furthermore, diurnal IOP measurement or 24-h IOP should be obtained to confirm the IOP being consistently <21 mmHg. It is important to differentiate nonglaucomatous optic neuropathies, such as congenital and hereditary anomalies of the optic disc, compressive lesions of the chiasm and optic nerve, and ischemic optic neuropathy from true NTG. A neuroimaging evaluation is highly suggested in a younger patient with significant decrease in visual acuity, reduction of color vision, pallor of the neuroretinal rim, highly asymmetric cupping, and VF defects respecting the vertical meridian. Although NTG shares the similar features of optic neuropathy with POAG, some differences exist in
structural abnormalities and VF defect. NTG has a higher incidence of disc hemorrhage (DH) compared with POAG. DH is an important risk factor for the onset and progression of glaucomatous optic neuropathy, especially in NTG. Narrower neuroretinal rim width at the baseline, history of migraine, low mean OPP, and the use of systemic beta blockers were the independent risk factors for DH occurrence in treated NTG patients. NTG seems to have a larger and deeper optic disc cupping and thinner neuroretinal rim, particularly in the temporal and inferior zones. By using optical coherence tomography (OCT), the macular ganglion cell complex loss was more localized in the inferior hemifield in NTG patients and more diffused in the high-pressure POAG patients.

Furthermore, NTG patients showed significantly deeper and closer-to-fixation scotomas in VF defects compared with high-pressure POAG. VF of NTG patients showed a higher percentage of abnormal points in the upper and lower central region. Because of the higher occurrence of central VF defect in NTG, the standard 10-2 strategy would be better than the 24-2 strategy, which may miss important VF defect in the central region. Despite relatively slow progression in NTG patients, the VF does develop or progress in approximately half of patients during follow-up. The Collaborative NTG Study Group reported that the risk factors for the VF progression were female sex, migraine, and occurrence of optic DH. Therefore, it is crucial to monitor the changes of the optic nerve and RNFL through ophthalmoscope, red-free RNFL photography, OCT and standard automated perimetry.

**Management**

Lowering IOP is the gold standard treatment for all types of glaucoma. From the results of Collaborative NTG Study Group, a 30% IOP reduction favorably influenced the disease course in NTG patients compared with untreated controls. The Low-pressure Glaucoma Treatment Study reported patients treated with brimonidine 0.2% were less likely to have VF progression than patients treated with timolol 0.5%. However, with more participants dropping out of the brimonidine group (55%) than the timolol group (29%), the conclusion should be interpreted more cautiously. Beta-blocker eyedrops may induce a significant drop in diastolic BP at night. NTG eyes receiving beta-blocker eyedrops showed VF progression significantly more often than those not receiving beta-blockers. The use of beta-blocker eyedrops may be a potential risk factor by aggravating nocturnal arterial hypotension. The prostaglandin analogs are, by far, the most popular choice of drug for the management of NTG. The new Rho-associated protein kinase inhibitors have been approved in the USA for IOP reduction in patients with open-angle glaucoma or ocular hypertension. Rho-associated protein kinase inhibitors could lower IOP by increasing aqueous humor outflow through the trabecular meshwork. They also offer the possibility of neuroprotection, a favorable impact on ocular blood flow, and even an antifibrotic effect.

Studies of selective laser trabeculoplasty for NTG have revealed the average IOP reduction was 14.7% and medication reduction was 26.7% from prestudy levels at 12-month follow-up. At 24-month follow-up, there was an 11.5% reduction in IOP and 41.1% reduction in glaucoma medication usage compared with prestudy levels. For NTG patients with inadequate IOP control with maximal medications or nonresponders to laser trabeculoplasties, trabeculectomy should be considered. Surgery is usually a great challenge because it requires the pressures of a single digit level without any hypotony. Using tighter scleral flap suturing technique is suggested to avoid overfiltration. In a study of NTG patients followed up over 15 years, IOP was decreased from a baseline of 14.7 mmHg to 9.1 mmHg and the slope of mean deviation of VF was significantly decreased from −0.86 dB/year to −0.19 dB/year after trabeculectomy.

Recently, minimally invasive glaucoma surgeries such as iStent and Xen offer less invasive modalities, which may have a potential role in the treatment of NTG. However, more prospective clinical studies and long-term follow-up are needed to evaluate their efficacy and safety in NTG.

Regarding neuroprotection, statins seems to reduce the risk of glaucoma by protecting cortical neurons from glutaminergic neurotoxicity and apoptosis. A prospective clinical trial has shown that simvastatin provides protection for NTG patients. The use of neurotrophins has also demonstrated clinical evidence of neuroprotection with improvement in visual acuity, VF and contrast sensitivity in glaucoma. When considering dietary supplements for glaucoma, Ginkgo biloba is a potential candidate. Previous literature has shown its antioxidant effects and increased ocular blood flow after using Ginkgo biloba. However, solid evidence is lacking due to the inclusive effect of Ginkgo biloba on the clinical outcomes in glaucoma patients.

**Conclusion**

NTG is within the spectrum of open-angle glaucoma, but the IOP is consistently <21 mmHg. The prevalence of NTG is higher in Asians compared with Caucasians. Current data have suggested that NTG may have different pathogenic mechanisms compared with high-pressure POAG. In the case of low intracranial pressure, the increased TLPD may cause damage to the optic nerve.
The prevalence and types of glaucoma in Malay people: Relationship between intraocular pressure and therapies including the control of systemic risk factors or improving ocular perfusion may be beneficial for the treatment of NTG.

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Conflicts of interest
The author declares that there are no conflicts of interests of this paper.

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