Review Article

Update on Normal Tension Glaucoma

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Abstract

Normal tension glaucoma (NTG) is labelled when typical glaucomatous disc changes, visual field defects and open anterior chamber angles are associated with intraocular pressure (IOP) constantly below 21 mmHg. Chronic low vascular perfusion, Raynaud`s phenomenon, migraine, nocturnal systemic hypotension and over-treated systemic hypertension are the main causes of normal tension glaucoma. Goldmann applanation tonometry, gonioscopy, slit lamp biomicroscopy, optical coherence tomography and visual field analysis are the main tools of investigation for the diagnosis of NTG. Management follows the same principles of treatment for other chronic glaucomas: To reduce IOP by a substantial amount, sufficient to prevent disabling visual loss. Treatment is generally aimed to lower IOP by 30% from pre-existing levels to 12-14 mmHg. Betaxolol, brimonidine, prostaglandin analogues, trabeculectomy (in refractory cases), systemic calcium channel blockers (such as nifedipine) and 24-hour monitoring of blood pressure are considered in the management of NTG. The present review summarises risk factors, causes, pathogenesis, diagnosis and management of NTG.

Keywords: Normal Tension Glaucoma; Ocular Hypoperfusion; Vasospasm

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INTRODUCTION

Normal tension glaucoma (NTG) is an optic neuropathy associated with glaucomatous optic nerve head damage, progressive retinal nerve fiber layer thinning, characteristic visual field defects, open anterior chamber angles on gonioscopy and maximum intraocular pressure (IOP) below 21 mmHg.[1]

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Glaucoma is a major optic neuropathy characterized by significant death of retinal ganglion cells.[2] According to global surveys, the second leading cause of blindness after cataracts is glaucoma.[3] Glaucoma affects more than 66 million people and is the second leading cause of visual loss worldwide.[4,5] NTG accounted for 92% of primary open-angle glaucoma (POAG) in a Japanese population.[6]

RISK FACTORS

- Patients with NTG tend to be older than those with primary open angle glaucoma (POAG)
- Female subjects have a higher prevalence of the disease than male counterparts

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- NTG is more frequent among Japanese people[7]
- The most important risk factor for glaucoma is elevated IOP. It has been established that high IOP is a part of the pathogenic process of NTG;[8] however, the pressure theory cannot sufficiently explain how NTG causes loss of vision. Multicenter clinical trials have confirmed the value of reducing IOP both in POAG[9,10] and NTG.[11,12] There is yet to be a consensus regarding the specific relationship between IOP and NTG. However, in many cases the progression of GON has been observed even after lowering IOP. Patients with NTG have wider diurnal fluctuations of IOP as compared to the healthy population.[13] IOP spikes may occur at night, and thus IOPs measured during office hours may miss nocturnal spikes in many patients.[14] Associated changes in nocturnal orbital blood pressure and IOP may affect optic nerve head blood perfusion differently in glaucomatous eyes as compared to healthy eyes, and this issue may also influence the susceptibility of the optic nerve to damage
- Central corneal thickness (CCT) in patients with NTG is lower than POAG subjects[15]
- Vascular dysfunction and ischemia have been considered as important factors in the progression of NTG.[16-19] However, the ischemia in glaucoma is not simply insufficiency of blood flow, but also due to improper vascular autoregulation,[20-22] and hypothetically episodes of transient ischemia and re-perfusion injury occur[23]
- Cold hands and feet, as an over-reaction to cold or stress, are suggestive of defective vasoregulation. Abnormal vasoregulation such as Raynaud's phenomenon and migraine are more associated with NTG than POAG. A study of peripheral vascular endothelial function in patients with NTG found impaired acetylcholine-induced peripheral endothelium-mediated vasodilation in comparison to healthy age- and sex-matched control subjects,[24] and polymorphisms of the endothelin receptor type A gene have been associated with NTG[25]
- Patients with NTG have an increased frequency of headaches with or without migraine features[26]
- Non-IOP-related cardiovascular dysregulation factors, such as systemic hypertension, systemic hypotension, nocturnal hypotension, and cardiac arrhythmia are implicated in NTG
- There are reports suggesting that signs of glaucoma in certain eyes may be related to an acute ischemic episode (shock-induced neuropathy),[23] or chronic obstructive arterial disease,[27,28] which may be non-progressive
- Mojon et al suggested that patients with sleep apnea syndrome are at high risk for glaucoma.[29] The prevalence of obstructive sleep apnea syndrome (OSAS) was higher in patients with NTG.[30] OSAS may cause optic nerve head hypoperfusion and glaucomatous optic neuropathy by creating transient hypoxemia and increasing vascular resistance
- Abnormally low diastolic double product (dDP = diastolic blood pressure × heart rate) may represent a state of cardiovascular autonomic dysregulation, resulting in low ocular perfusion in certain NTG patients[31]
- NTG patients with lower heart-rate variability, which reflects autonomic dysfunction with sympathetic predominance, manifested a faster rate of central visual field progression as compared to patients with higher heart-rate variability[32]
- Glaucoma patients have a decrease in central retinal vein (CRV) blood velocities. Spontaneous venous pulsation is less prevalent in glaucoma patients than in healthy individuals. This is particularly important in NTG patients[33]
- Duplication of the TANK-binding kinase 1 (TBK1) gene can be a rare cause of NTG[34]
- Lifestyle factors such as smoking and high body mass index can cause progression of glaucomatous visual field defect. In the Blue Mountain Eye Study, smokers were found to have higher IOP than non-smoker counterparts[35]
- Out of the metabolic syndrome components, hypertension and impaired glucose tolerance (IGT) may contribute to an increased risk of NTG.[36]

DIAGNOSIS

History has to be taken regarding migraine, Raynaud`s phenomenon, episodes of shock, head injury, headache and other neurological symptoms. Use of medications including systemic steroids and antihypertensive agents such as beta blockers should also be taken into account.[7]

Goldmann applanation tonometry, gonioscopy, stereoscopic biomicroscopy of the optic nerve head, optical coherence tomography and Humphrey field analyser are the main tools of investigation for diagnosis of NTG. IOP is usually in the higher teens but may rarely be in low teens.

Increased cup to disc ratio or asymmetry of cupping between the two eyes (difference more than 0.2) is significant [Figure 1]. A region of absent retinal pigment epithelium (RPE) is more often seen as a crescent or halo at the disc border in NTG. The cupping is often worse in the region of absent RPE, with field loss more marked in the corresponding region.[37-39] Occasionally, there is a notch due to thin or absent neuro-retinal rim, referred as a "focal ischemic" type of cupping.[6] This is associated with a highly localized dense arcuate field defect or even a dense hemifield defect. Other discs have diffuse shallow cupping and pallor, leading to the designation "senile sclerotic" disc.

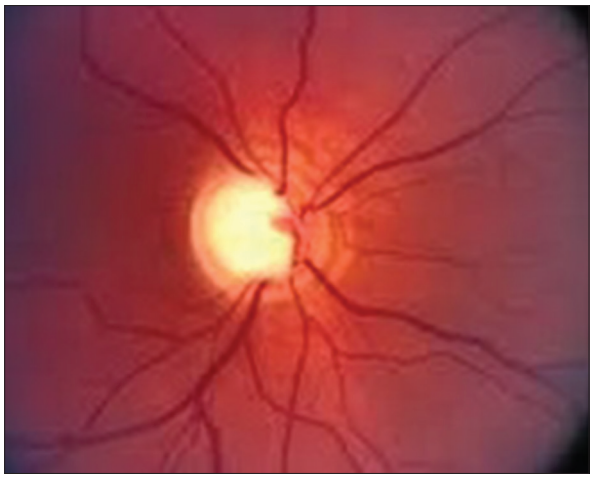

Figure 1. Optic disc in normal tension glaucoma.

Patients with high myopia may be particularly susceptible to NTG. With a frequent temporal crescent, scotomas tend to be closer to fixation than the paracentral scotomas of non-myope cases. Still other discs have cupping resembling ordinary glaucoma with mildly elevated IOP. Splinter hemorrhages are seen more commonly in NTG, but may also be found in POAG.[40] Hemorrhages may simply indicate poor control. Although the optic nerve head may be larger in NTG than in POAG, glaucomatous cupping is comparable. Normal-tension glaucoma eyes can have greater optic nerve head (ONH) torsion as compared to POAG eyes with matched axial length. The direction of the ONH tilt and torsion can be related to the location of the visual field defect only in NTG eyes.[41] As compared to normal subjects, peripapillary choroidal thickness was significantly thinner in NTG patients, at least in some locations.[42]

Visual field defects in NTG are essentially comparable to POAG. In general, patients with NTG appear to have deeper, more localized scotomas.[43] One study found a significantly greater rate of progressive visual field loss in NTG.[44] Another revealed a difference in the progression pattern as compared to POAG patients; in POAG eyes, field defects initially increased in area and later in depth, whereas in patients with NTG, the increases in area and depth remained in constant proportion.[45]

Other investigations include 24-hour blood pressure monitoring to exclude nocturnal systemic hypotension; blood tests to rule out other causes of glaucomatous optic neuropathy such as vitamin B12 and folate levels, ESR/CRP and serum ACE. Cranial MRI may be necessary to rule out intracranial space occupying lesions (SOLs); and nail fold capillaroscopy with cold provocation may detect blood flow abnormalities.[7]

DIFFERENTIAL DIAGNOSIS

A number of congenital disorders may be confused with NTG; these include optic nerve anomalies including coloboma, pits, oblique insertion of the optic nerve, in addition to autosomal dominant optic atrophy (Kjer type). Acquired disorders which need to be considered in the differential diagnosis of NTG include history of steroid use by any route which may have led to prior elevated IOP, prior trauma or surgery which may have caused elevated IOP, hemodynamic crisis, methyl alcohol poisoning, optic neuritis, ischemic optic neuropathy (both arteritic and non-arteritic), compressive lesions of the optic nerve and tract (e.g., meningioma, vascular lesion); and wide diurnal fluctuation in IOP.[46]

TREATMENT

The main goal of glaucoma treatment is IOP reduction. The Early Manifest Glaucoma Trial showed that glaucoma progression was decreased by 10% with reduction of each mmHg of IOP.[12] According to the Collaborative Normal Tension Glaucoma Study Group, an IOP reduction of 30% slowed the progression of normal-tension glaucoma.[16]

Choices for medical treatment in progressive cases include betaxolol eye drops which have a beneficial effect on optic nerve blood flow in addition to IOP reduction.[7] Other beta blockers and adrenergic drugs (such as dipivefrine) should better be avoided because of the probability of nocturnal systemic hypotension and optic nerve hypoperfusion. Prostaglandin derivatives tend to have greater IOP lowering effect which may be of overriding consideration.[7] Dorzolamide-timolol fixed combination (DTFC) is a safe and effective IOP-lowering agent in patients with NTG.[47] Brimonidine significantly improved retinal vascular autoregulation in NTG patients; however, short-term alterations in visual function could not be demonstrated.[48]

In the collaborative normal tension glaucoma study (CNTGS), 57% of the patients achieved 30% IOP reduction with topical medications, laser trabeculoplasty or both. The remaining 43% required filtering surgery which may prevent progressive damage.[49-52] A single session of selective laser trabeculoplasty (SLT) for NTG achieved IOP reduction of 20% from pre-study IOP and 30% reduction from baseline IOP at 6 months.[53] Surgery is considered if progression occurs despite medications and IOP reduction.[49] Deep sclerectomy seems to be effective and safe in reducing IOP in patients with NTG. Intraoperative use of MMC results in lower postoperative IOP after 12 months without an increased rate of complications.[54]

An additional part of managing NTG is treatment of any cardiovascular abnormality such as anemia, hypotension, congestive heart failure (CHF), transient ischemic attacks and cardiac arrhythmias to increase optic nerve head perfusion.[55] If significant nocturnal dips in blood pressure are detected, it may be necessary to reduce the antihypertensive medication especially at bedtime.[7]

Finally treatment is aimed at neuroprotection to improve the retinal ganglion cell or optic nerve head function. Nilvadipine, a calcium channel blocker, increases blood flow to the optic nerve head and fovea. There was a significant reduction in the rate of disc and field damage in NTG patients who received calcium channel blockers.[56-58]

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Conflicts of Interest

There are no conflicts of interest.

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