

Normal tension glaucoma: risk factors pertaining to a sick eye in a sick body

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Abstract

Normal tension glaucoma is a clinical condition, associated with a pathologically excavated optic disc and characteristic glaucomatous visual field loss that represents a diagnostic and therapeutic challenge for ophthalmologists. Apart from intraocular pressure, the clinical course of the disease shares similarities with that of primary open angle glaucoma. Therefore, some authors have questioned whether normal tension glaucoma is artificially distinct from primary open angle glaucoma by intraocular pressure, or represents a subset of disease in which patients show different patterns of optic disc damage and quantity and quality of visual field loss, possibly as a result of different mechanisms of damage. The literature appears to support the hypothesis that normal tension glaucoma and primary open angle glaucoma represent a continuum of open angle glaucomas, in which increased intraocular pressure is the predominant causative risk factor in primary open angle glaucoma, and factors in addition to intraocular pressure are important in normal tension glaucoma. This review will be published in 2 parts. Part 1 discusses the risk factors related to normal tension glaucoma. Part 2 will discuss a specific entity in normal tension glaucoma — disc hemorrhage. A Brief Report provides some approaches to the management of normal tension glaucoma.

Introduction

Since its original description by von Graefe in 1857,¹ normal tension glaucoma (NTG) has remained a diagnostic and therapeutic challenge for ophthalmologists. NTG is a clinical condition associated with a pathologically excavated optic disc and characteristic glaucomatous visual field loss. Apart from the intraocular pressure (IOP) being in the statistically ‘normal’ range, the clinical course of the disease shares similarities with that of primary open angle glaucoma (POAG). Some authors have questioned whether NTG merely represents an artificial distinction from POAG by the IOP² or represents a subset of disease along a continuum of which patients show a different clinical course as far as patterns of optic disc damage and quantity and quality of visual field loss are concerned,³ possibly as a result of different mechanisms of damage. The current literature appears to support the hypothesis that NTG and POAG represent a continuum of OAGs, in which a certain level of IOP is the predominant causative risk factor in POAG, while factors in addition to IOP are more important in NTG.⁴ There is considerable overlap between the 2 conditions. Additionally, within the population of patients with NTG, there are subsets in which blood flow and other factors may assume relative importance.⁴

This review is divided into 2 parts. Part 1 discusses the risk factors related to NTG. Part 2 discusses a specific entity in NTG — disc hemorrhage (DH). A Brief Report, also published in this issue of *Hong Kong Journal of Ophthalmology*, provides some approaches to the management of normal tension glaucoma.

Risk factors for having the disease

Risk factors, can be classified into 3 categories:

- risk factors for having NTG (Table 1)

Key words: Glaucoma, Glaucoma, open-angle, Intraocular pressure, Risk factors, Vascular diseases

Table 1. Risk factors for having normal tension glaucoma.

Age
Race
Myopia
Family history of glaucoma
Intraocular pressure level
Central corneal thickness
Cardiovascular system
Systemic hypertension
Systemic hypotension
Abrupt change of blood pressure (e.g., shock)
Nocturnal dips in blood pressure
Vasospasm
Vasospastic syndrome
Migraine
Raynaud's phenomenon
Obstructive sleep apnea syndrome
Immune system related
Monoclonal gammopathy
Coexisting autoimmune disease (e.g., rheumatoid arthritis)
Neurosensory hearing loss
Silent cerebral infarcts
Autonomic dysregulation syndrome

- factors that affect the rate of disease progression (Table 2)
- factors that relate to the degree of benefit derived from IOP lowering (Table 3).

These 3 categories of risk factors do not necessarily overlap.

The role of intraocular pressure

Until recently, an important question to address was whether IOP was truly involved in producing optic nerve damage, even when the IOP was in the statistically 'normal' range. The rationale for lowering IOP in patients with NTG was based on reports that suggested a correlation between asymmetric optic nerve damage and asymmetric IOP in patients with NTG, implying that an IOP within the statistically normal range still contributes to optic nerve damage.⁵⁻⁷ However, because of the previous lack of firm evidence for the role of IOP in the disease, clinicians often hesitated to provide aggressive IOP-lowering therapy. Consequently, when interventions appeared to be ineffective at halting disease progression, it was uncertain whether failure was due to ineffective lowering of IOP or to the possibility that IOP plays no role in the pathogenesis of the disease.⁸

Such confusion about the role of IOP lowering was finally settled after the Collaborative Normal-Tension Glaucoma Study;⁹ patients who had their IOP successfully lowered by 30% of their IOP at initial presentation demonstrated slower visual field progression than the untreated patients.⁹ At 3 years, 20% of the treated cohort and 40% of the untreated cohort experienced progression; at 5 years, a similar 20% of the treated cohort, but 60% of the untreated cohort, experienced progression.⁹

Age

Age is a known risk factor for NTG.¹⁰ NTG is considered to be a disease of elderly people. The mean age of onset in various studies ranged from 63.7¹¹ to 64.9 years,¹² and

Table 2. Factors that affect the rate of progression of normal tension glaucoma.

Intraocular pressure
Race (Caucasian)
Female sex
Migraine
Baseline optic disc hemorrhage
Recurrent optic disc hemorrhages
Central corneal thickness
Autonomic dysregulation syndrome

Table 3. Factors related to the degree of benefit derived from intraocular pressure lowering.⁸

No baseline disk hemorrhage
Female sex
Female sex with migraine
Small cup-disc ratio
Family history of glaucoma
No family history of stroke
No personal history of cardiovascular disease

the prevalence increases with age. In the Low-Pressure Glaucoma Treatment Study,¹² 9.5% of patients were aged 40 to 49 years; 16.3% were 50 to 59 years; 36.8% were 60 to 69 years; and 29.5% were 70 to 79 years.

Genetics

There are reports on the genetic associations of NTG,¹³⁻¹⁷ although the situation remains unclearly defined. There are various reports on polymorphism of the OPA1 gene, suggesting that OPA1 association may be limited to NTG but not POAG.^{13,14} More recently, the D2S176 marker on GLC1B locus on Ch2 has been implicated in NTG.¹⁵ Multiple single nucleotide polymorphisms (rs10759930, rs1927914, rs1927911, rs12377632, rs2149356, and rs7037117) in the TLR4 gene are associated with the risk of having NTG.¹⁶ There is also a report on the association with Glu50Lys OPTN sequence variation for familial NTG, a rare form of the disease.¹⁷

Studies have shown that the following are not associated with NTG: WD repeat domain 36 gene (WDR36) sequence alterations¹⁸ and interleukin-1- β polymorphism.¹⁹ In a previous study, we found that the apolipoprotein E epsilon 4 allele confers a protective effect against NTG.^{20,21} More studies will be needed to determine exactly how genetics is related to onset of NTG.

Central corneal thickness

The importance of central corneal thickness (CCT) has been emphasized, as CCT influences the accuracy of tonometric measurement,²²⁻²⁸ with thick corneas exaggerating the true IOP values and thin corneas underestimating them. More importantly, a thin CCT has been suggested to be an independent risk factor for the development and progression of glaucoma.^{23,26-28} In our group of patients with NTG, the hazard ratio was 1.35 per 30 μ m thinning,²⁹ and the odds ratio was 1.41 per 40 μ m thinning according to the Barbados Eye studies.³⁰ It is likely that a thin CCT is a surrogate for a

vulnerability factor for optic nerve head damage, and such vulnerability is unlikely to be a mere underestimation of true IOP, which results in delayed diagnosis or inadequate lowering of IOP.

Risk factors related to the cardiovascular system

Circulatory pathophysiology is known to influence the pathogenesis of glaucoma. Disturbance of the circulatory physiology should logically affect blood perfusion to the optic nerve, despite the presence of an autoregulatory system. Felix Lagrange of Bordeaux was the first to note that glaucomatous optic neuropathy may in fact be a 'sick eye in a sick body' as early as 1922.³¹ Kummell, in 1911, was one of the first authors to describe the relationship between high blood pressure (BP) and glaucoma.³² Thereafter, numerous studies have demonstrated the correlation between arterial hypertension and glaucoma,³³⁻⁴¹ as well as between arterial hypotension and glaucoma.^{40,42-45} Patients with NTG or POAG have been shown to be more likely to have hypertension than healthy controls. We know that the relationship between hypertension and mean ocular perfusion pressure is not straightforward, and simple hypertension does not lower the mean ocular perfusion pressure. In fact, assuming the same vascular tone and intact autoregulatory mechanism, a modest increase in BP may slightly increase the ocular perfusion pressure. However, the *treatment* of hypertension has been shown to be the culprit in resulting NTG and optic nerve ischaemic damage. Hayreh et al performed an important study of 24-hour ambulatory BP monitoring and diurnal IOP curves.⁴² These researchers noted a significantly lower nighttime mean diastolic BP and a significantly greater mean percentage decrease in diastolic BP in patients with NTG.⁴² Moreover, patients with arterial hypertension taking oral hypotensive therapy, who developed nocturnal hypotension as a result, showed a significant association with glaucomatous visual field deterioration.^{42,46} Patients with NTG with deteriorating visual fields had lower nocturnal BP than those who had stable visual fields, and it was interesting to note that the other BP parameters did not differ significantly between the 2 groups.⁴⁷ Patients with pre-existing greater nocturnal systolic, diastolic, and mean arterial BP dips were more likely to develop visual field deterioration despite good IOP control.⁴⁸ Currently it is not entirely certain what would be the critical level of BP dip that would result in NTG and its deterioration. Further large-scale prospective studies will answer this important question. For the time being, we do not recommend routine 24-hour BP checks for all patients with NTG. However, for those patients with NTG with continual optic nerve glaucoma damage despite good IOP control, in the presence of hypertension, we may consider 24-hour ambulatory BP monitoring to look for a nocturnal dip (>20% from baseline is considered a large dip). In case such a dip exists, close liaison with our fellow physicians may be justified to *fine-tune* the BP control to avoid the optic nerve 'dying in the night'.

Vasospasm, migraine, and endothelin

Blood perfusion to the optic disc is also affected by the integrity of the autoregulatory system. It is interesting to note that

vasospasm is not only related to the blood supply to the optic disc, but also renders the eye more sensitive to both IOP increase and blood pressure decrease.⁴⁹ Indeed, vasospastic syndrome, a heterogeneous condition that leads to microvascular dysregulation, is now an established major risk factor for glaucoma.^{50,51} It was also found that involvement of acral vasospasm (i.e., a reduction of nail-fold capillary blood-flow velocity with cold provocation) is higher in patients with NTG than those with high-tension glaucoma.⁵² Also, there may be an association between choroidal vasospasm and vasospasm in the fingers.⁵³ In the presence of vasospasm, the ability to alter the diameter of the small blood vessels might be impaired, thus affecting the blood supply when the perfusion pressure is reduced through either an increase in IOP or decrease in BP or both, thereby increasing susceptibility to damage by these 2 factors.¹¹

Similarly, functional vasospasm of the brain vessels is linked to the pathogenesis of migraine. In fact, both NTG and migraine are associated with systemic vascular dysregulation.⁵³ Phelps and Corbett found a higher prevalence of migraine-like headaches in patients with NTG than in patients with open angle glaucoma or healthy controls.⁵⁴ Details of vasospastic disorder have been reviewed elsewhere.^{55,56} It is important to emphasize that vasospastic syndrome does not equate to Raynaud's phenomenon or migraine. Although patients with migraine are more likely to have vasospastic syndrome than the general population,⁵⁷ not all patients with vasospastic syndrome have migraine and vice-versa. Similarly, patients with vasospastic syndrome often present with cold hands, but rarely have clinical Raynaud's phenomenon.⁵⁶ This may explain why migraine is established as a risk factor for NTG, whilst the association between NTG and Raynaud's phenomenon remains questionable, even though Raynaud's phenomenon is generally identified as an important risk factor.

One of the known mechanisms of vasospasm is related to endothelin-1 (ET-1). ET-1 is increased in patients with primary or secondary vasospasm. ET-1 is a peptide that interferes with the intracellular contractile mechanism by increasing the sensitivity of the arteries towards calcium. Therefore, not surprisingly, ET-1 may also induce a vascular hyper-responsiveness to various stimuli such as cold.⁵⁶ As we shall see in the subsequent section, this could have a relationship with obstructive sleep apnea (OSA).

Obstructive sleep apnea syndrome

Various studies have suggested a significant association between OSA and incidence of NTG and open angle glaucoma.^{58,59} Visual field loss and optic disc damage is related to the Respiratory Disturbance Index during night sleep.⁶⁰

Whilst the exact mechanism of OSA causing optic nerve damage is yet to be determined, several hypotheses have been suggested. Optic nerve damage might be caused by impaired blood perfusion to the optic nerve head, resulting either directly from OSA, or from OSA-induced arterial hypertension and arteriosclerosis.⁶⁰ Another suggestion came from the

observation that patients with OSA have an increased plasma ET-1 level,⁶¹ which is not surprising, as hypoxia would lead to decreased production of endothelium-derived nitric oxide, which in turn would decrease its effect on vasodilatation, as well as downregulation of ET-1 production.

Silent cerebral infarct

Silent cerebral infarct (SCI) is defined as a brain infarct resulting from vascular occlusion that is found incidentally by magnetic resonance imaging (MRI) or computed tomography (CT) in the absence of clinically detectable focal neurological signs in otherwise healthy people or during autopsy. SCI is an important risk factor for further stroke.⁶² MRI studies of the brain have revealed evidence of frequent vascular insults in patients with NTG,⁶³ which has been subsequently echoed by other studies demonstrating that ischaemic changes could be found in as many as 34% of patients with NTG with MRI imaging.^{64,65} Such a correlation with NTG is understandable if the optic nerve is considered to be part of the central nervous system (CNS), as they are exposed to the same risk factors; vascular insults to the CNS would probably cause the same insults to the optic nerve, resulting in poor perfusion and an increased risk of NTG. We conducted a prospective cohort study of 286 eyes with NTG.²⁹ After 3 years of follow-up, SCI was present in 29.6% of patients with visual field progression versus 15.3% of patients with stable visual fields ($p = 0.004$).²⁹ Kaplan-Meier survival analysis revealed 65.6% of SCI-positive patients versus 45.9% of SCI-negative patients progressed ($p = 0.003$). Cox proportional hazards regression analysis showed disc hemorrhage (hazard ratio [HR], 2.28; 95% confidence interval [CI], 1.54-3.37; $p < 0.001$), SCI (HR, 1.61; 95%CI, 1.09-2.36; $p = 0.016$), systemic hypertension (HR, 1.48; 95%CI, 1.04-2.10; $p = 0.029$), and CCT (per 30 μm of thinning: HR, 1.35; 95%CI, 1.16-1.75; $p < 0.001$) were associated with visual field progression.²⁹ Prevention of SCI has been shown to decrease the incidence of strokes. If SCI is also an independent risk factor for visual field progression, prevention of SCI may slow visual field progression. This could have implications for future NTG treatments and deserves further evaluation.²⁹

Optic disc hemorrhages

Disc hemorrhage is associated with the prevalence of NTG.⁶⁶ It is also important to note that such hemorrhage may occur with posterior vitreous detachment, optic disc drusen, other causes of optic neuropathies, and vascular occlusive diseases. Therefore, while the finding of optic disc hemorrhage is alarming, it needs to be carefully considered with other clinical parameters before a diagnosis is made. The significance of disc hemorrhage will be discussed in the next section.

Factors that affect the rate of progression of normal tension glaucoma

As mentioned earlier, significant lowering of IOP slows the progression of NTG.⁹ Therefore, at least in NTG, the level of IOP not only affects the risk for an individual to have the disease, but also affects the rate of deterioration. However, the outcomes for individual patients are highly variable;

whilst some 20% of treated patients experience continuous deterioration, more than half of untreated patients have a static course over 5 to 7 years. It is uncertain whether IOP itself may explain the variability or whether other non-IOP-related risk factors account for such an observation.

In response to this observation, a follow-up study was performed to identify the risk factors for progression of the disease,¹¹ especially those that affect the prevalence of glaucoma. Visual field data of 160 patients who were enrolled in the Collaborative Normal Tension Glaucoma Study⁸ and had a period of time without IOP lowering during the study were included in the analysis. The end-point of disease progression was in accordance with the criteria of glaucomatous visual field progression that was used in the parent study.⁹ The data were assessed by various statistical methods.

With Kaplan-Meier analysis and comparison of the mean survival time, race, sex, migraine, and baseline disc hemorrhage were identified as factors that predict for a progressive course of disease. Untreated women were shown to have a more rapid course of disease progression than untreated men. It was also observed that patients with migraine, who were almost entirely women in the study, had a significantly faster course of deterioration. With the consideration that either of these factors might act as a confounding factor, another comparison of sex within the patients without migraine was performed. Women showed more rapid progression than men; similarly, untreated women with migraine also showed a more rapid progression when compared with untreated women without migraine. However, neither comparison demonstrated statistically significant results. On the other hand, the numbers of patients in each subgroup were small, and further investigation into these factors may be worthwhile. It is also interesting to note that, although migraine as a risk factor for disease progression may be related to the underlying vasospastic mechanism, Raynaud's phenomenon did not turn out to show any correlation with the course of the disease; this emphasizes vasospastic syndrome as a continuous spectrum of disease.

In this study, baseline disc hemorrhage was shown to be highly significant for disease progression by multivariate survival analysis, signifying that it is an additional and independent risk factor. This echoes with the previous studies that also demonstrated disc hemorrhage to be a poor prognostic factor for NTG.^{67,68}

Furthermore, this study also demonstrated a faster rate of disc hemorrhage occurrence in patients with progressive disease. The number of hemorrhages is also higher within this group. However, the role of recurrent disc hemorrhages (i.e., increasing number of disc hemorrhage) as a predictor for glaucomatous progression remains controversial. Some researchers have reported no difference between a single disc hemorrhage and recurrent disc hemorrhages in terms of both rate of progression of optic disc shape or visual field defects.⁶⁹ Another study showed that recurrent disc hemorrhages increase the risk of retinal nerve fiber layer (RNFL)

deterioration, but failed to demonstrate such a correlation in terms of visual field defects.⁷⁰ Other researchers have demonstrated more pronounced progressive visual field changes in eyes with recurrent disc hemorrhages.⁶⁸

It has been shown that Asian patients with NTG have a significantly longer estimated mean survival time (time to progression) than Caucasian patients.¹¹ We believe that more studies are warranted to confirm this.

As mentioned earlier, a thin CCT was shown to increase the chance of progression of the disease.

Factors that relate to the degree of benefit derived from intraocular pressure lowering

As previously mentioned, 20% of treated patients still experience continuous progression of the disease; it is therefore uncertain whether IOP alone is the cause. Consequently, another follow-up study was performed to identify factors that predict the benefit of lowering IOP in patients with NTG.⁷¹ 144 patients were included in this analysis, all of whom had been recruited to the initial Collaborative Normal Tension Glaucoma Study;⁸ 64 patients had their IOP successfully lowered by 30% from baseline levels and 80 had been randomized not to be treated. Univariate Kaplan-Meier analysis and regression analysis of the mean defect index were used and identified the predictive factors, as listed in Table 3. The statistical significances for these factors were not strong, as the subgroups were small. However, they provide trends that reflect various aspects of NTG that is worthy of further discussion.

A statistically significant treatment benefit was observed in the subgroup of patients without baseline disc hemorrhage. In contrast, in patients with baseline splinter hemorrhages, there were no statistically significant differences between the treated and untreated groups.

When comparison of female patients was made, treated patients had a significant benefit over untreated patients. This was not demonstrated among the male patients. Comparison was also attempted to evaluate migraine as an independent predictive factor. However, comparison was only made amongst the female patients since almost all patients with migraine in this study were women. Not surprisingly, both subgroups showed significant benefit, and it was inconclusive as to whether IOP lowering truly affects the contributing glaucomatous pathophysiology of migraine and thus resulted in a beneficial effect, or whether IOP lowering merely affects the pathogenic factors associated with female sex. Moreover, a history of vasospasm did not emerge as having a relationship with benefit from lowering the IOP in this study.

A small cup-disc ratio (CDR; vertical, ≤ 0.8 ; horizontal, ≤ 0.7) was found to manifest significant benefit from lowering IOP, although the treatment effect could not be established statistically among patients with large CDRs (both vertical and horizontal). However, interpretation of this result is difficult, as it might be confounded by more variable visual field threshold values in advanced disease, so much so that it

could easily trip the progression criterion falsely. Considerably more detailed statistical analysis would be necessary to review a true different rate of progression in the early or advanced stages of the disease.

Patients with a family history of glaucoma, without a family history of stroke and/or without a personal history of cardiovascular disease, also benefited from IOP lowering. This might be a reflection of the underlying genetic factors that are involved, not only in the disease process, but also in the susceptibility of the optic nerve to damage by IOP.

It is possible that NTG is a heterogeneous group of diseases that produce similar clinical outcomes as a result of various etiologies. As described previously, factors such as cardiovascular, vasospastic, and autoimmune diseases may contribute to the pathogenesis of NTG. However, the weight of contribution for each factor may be different for individual patients. Previous observations showed that women who have migraine, cold hands and feet, and disc hemorrhages often have purely localized disc defects, whereas older patients with hypertension and cardiovascular disease often have an atrophic disc.⁷² Although the strength of such associations is yet to be confirmed, such observation suggests that the etiologies for patients with NTG are heterogeneous; the same applies to factors among the different patient groups that affect the disease pathogenesis. This would explain the variation between different 'types' of NTG in terms of disease progression, as well as benefit gained from IOP lowering. In the Collaborative Normal Tension Glaucoma Study,⁸ patients who had cardiovascular disease demonstrated a slow progression, whereas those untreated patients with migraine showed the most rapid progression. In terms of benefit gained from IOP lowering, previous evidence suggests that the clinical course of glaucoma patients with occlusive vascular disease is less affected by IOP. In contrast, those patients with vasospastic vascular disease had the most severe glaucomatous damage that was related to the highest recorded IOP,⁷³ although this correlation might be questionable.⁷¹

It is possible that patients with vasospastic disease have factors that affect autoregulation of vessels that are related to the IOP level, whereas patients with occlusive vascular disease have ischemic optic disc damage independent of IOP effects.⁷¹ Equally, patients who have a family history of stroke and/or a personal history of cardiovascular disease might also have similar factors, which might explain their lack of benefit from IOP lowering. Confirmation of this correlation in future study may provide tailor-made therapy for individual patients with NTG.

Conclusions

We have discussed 3 different types of NTG factors: risk factors of having the disease aids identification of patients and subsequent treatment. Factors that predict disease progression and factors that suggest benefits derived from IOP lowering provide prognostic values for individual patients. It must be emphasized that these types of risks are different, although some of them overlap.

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