Is “normal tension glaucoma” glaucoma?

Ning Fan\textsuperscript{a}, Junkai Tan\textsuperscript{b}, Xuyang Liu\textsuperscript{b,⁎}

\textsuperscript{a} Shenzhen Eye Hospital, School of Optometry, Shenzhen University, China
\textsuperscript{b} Xiamen Eye Center, Xiamen University, China

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ABSTRACT

Primary open angle glaucoma (POAG) represents a distinct disease entity with elevated intraocular pressure (IOP) as the main risk factor, even though the reasons for why the IOP is elevated remains to be elucidated. It is considered that normal tension glaucoma (NTG) is a subtype of POAG, comprising a special form of glaucomatous neurodegeneration or glaucomatous optic neuropathy (GON) almost exactly the same as that seen in POAG, but the IOP, as named, remains in the statistically normal range. Actually the disease entity of NTG has been a profound confusion and it is difficult to be accurately conceptualized. One of the reasons is that the IOP is closely linked to the occurrence of GON in POAG but not in NTG, and for the latter, it seems that GON is secondary to a number of local or systemic disorders. In recent years, increasing evidences suggest that NTG or IOP independent GON is a non-glaucomatous disease with different disease entities from POAG and with more diverse and complex etiologies. Here we hypothesized that NTG, at least for those with recognizable primary diseases, is not a glaucomatous disease; instead, it represents a group of disorders with GON as a characteristic clinical feature or phenotype.

Introduction

IOP and its significance to pathogenesis of POAG and NTG

Primary open-angle glaucoma (POAG) is a leading cause of irreversible blindness with elevated intraocular pressure (IOP) as the major risk or disease causing factor. IOP is mainly determined by the production and drainage of aqueous humor. The normal IOP plays a key role in maintaining the physiology and function of the eye. It is generally accepted that, based on epidemiological, pathological and molecular genetic studies, elevated IOP is a cause or major risk factor associated with glaucomatous optic neuropathy (GON) of POAG \cite{1-5}. No matter how many risk factors can be listed in the pathogenesis of POAG, if the IOP is normal, the diagnosis of POAG cannot be made. The randomized controlled trials (RCTs) have demonstrated that IOP reduction reduces the incidence and the progression rate of glaucoma \cite{6,7}. However, the basis for why and how the IOP is elevated remains unclear in POAG, and that is why it is called “primary” disease. Previous studies suggested that the trabecular meshwork and juxtacanalicular tissue in conventional outflow pathway may become dysfunctional, congested and deposited with excess extracellular matrix, leading to an increase in resistance to outflow through the conventional pathway, and in IOP in eyes with POAG \cite{8,9}.

Therefore, glaucoma is an optic neuropathy mainly caused by elevated IOP, even though the mechanism underlying the elevated IOP induced optic nerve damage remains not completely clear. The elevated IOP may injure the optic nerve by mechanically distorting and/or stretching the retinal ganglion cell (RGC) axons, which are unmyelinated and vulnerably to damages, at the site of lamina cribrosa (LC). It is speculated that the elevated IOP may cause matrix metalloproteinases (MMPs) release, which in turn disaggregate and weaken the LC tissue, resulting in stretching and bending of RGC axons and disturbance of the blood vessels supplying the optic nerve and the globe \cite{10,11}. Other mechanisms, including chemical, bioenergetic and local environmental conditions/insults, by which the elevated IOP functions as a causative factor to induce GON, have been reviewed previously \cite{12-15}.

NTG is previously and currently classified as a subtype, or to be within the continuum, of POAG. One of the main considerations is that the normal IOP may function as more or less the same as elevated IOP to the eyes with NTG. In other words, the patients with NTG may have a lower threshold for IOP induced mechanical injury than normal eyes and those with POAG, indicating that the mechanisms discussed above for POAG are also applicable to NTG. However, in NTG, the pressure theory fails to explain how the normal IOP causes injuries to RGC axons \cite{15}. Up to date, there is no evidence showing that the normal IOP is
Collaborative Normal Tension Glaucoma Study (CNTGS) compared two groups of NTG with or without IOP lowering treatment, and found no correlation with IOP levels maintained during the follow-up between the two groups, and no benefit of treatment in the intent-to-treat analysis either [16].

Although the role of IOP cannot be completely ruled out yet in the pathogenesis of NTG, increasing evidences reveals that IOP-independent mechanisms including vascular factors, ocular blood flow, intracranial hypotension, endothelial dysfunction, neurovascular factors, autoimmune and genetic background, may be crucial in the development of GON in NTG [17,18].

GON can be seen in a number of disorders, and glaucoma is just one of them. In another word, maybe a more straightforward point should be made, stating that “glaucomatous optic neuropathy (GON)” is not a very accurate term, which may easily cause confusion and misdiagnosis, leading to improper management, and influence the re-cognition of the true disorders behind. Previous studies indicated that almost one quarter of the eyes with GON were misdiagnosed as NTG when evaluated even by glaucoma specialists [19].

Given the fact that the IOP is within statistically normal range, the disease-initiating factor(s) for NTG remains elusive. It has been chronicled that damage to the RGC axons that form the optic nerve causes retrograde and anterograde demise of the corresponding RGC bodies. It is possible that the RGCs themselves are simultaneously and deleteriously impacted by their environment that may contain low oxygen, depleted energy sources, and high levels of damaging neurotoxins and inflammatory cytokines [16-18].

Kim et al classified NTG patients into two distinct subgroups with cutoff IOP of 15 mmHg: low-teen group (IOP ≤ 15 mmHg) and high-teen IOP (15 mmHg < IOP ≤ 21 mmHg). Interestingly, there were more Raynaud phenomenon, a peripheral vasoconstrictive response to cold temperatures and/or emotional stress, observed in the low-teen IOP group than in the high-teen group, indicating a link between the progression of NTG and peripheral vasospasm and other mechanisms underlying the Raynaud phenomenon, in low-IOP patients, and IOP is not actively involved in the pathogenesis of NTG, at least in those with relatively low IOP [20].

Therefore, NTG can be mainly classified under vascular category. Our question is whether NTG or GON is a primary disease or it is just a result or phenotype of a number of diseases capable of impairing autoregulatory capacity of ocular blood vessels.

Phenotypic differences between NTG and POAG

Though the pathologic mechanisms of both NTG and POAG remain unclear, significant differences in the prevalence and clinical features between these two diseases were observed.

The prevalence of NTG

It is generally accepted that the risk factors of NTG include gender (more in female), race (more frequently seen in Japan than in European and American countries) [17]. The Japanese Tajimi study showed that the prevalence of POAG was 3.9%, of which 92% had an IOP of 21 mmHg or less [21]. Similarly, a study in Sangju (a rural Korean town) showed that 94.4% of POAG cases with IOP of less than 21 mmHg [22]. A Chinese population-based study showed that about 80% of patients with POAG had maximum IOPs of 21 mmHg or less over a 24-hour period. Twenty-four-hour IOP was similar between two groups, and no benefit of treatment in the intent-to-treat analysis either [16].

These results suggested that Asian population appears to be especially susceptible to NTG, and factors other than IOP may play an important role in the development of GON. It is noteworthy that some vascular failures related systemic disorders share a similar trend to that of NTG. Vasospasm was more commonly observed in Japanese than in European and American patients [17], and migraine was characterized as a vasospastic disorder and commonly seen in women [24].

Studies showed that the impaired vascular autoregulation was more pronounced in NTG than in high tension glaucoma (HTG), especially more pronounced in NTG cases with progressive GON than those with relatively stable status [17]. Therefore, the ocular blood flow may play an important role in pathogenesis of NTG or GON.

Clinical features

NTG is known as a multifactorial optic neuropathy characterized by progressive RGC death and glaucomatous visual field loss, sharing the same GON as that of POAG. Both the NTG and POAG are characterized by optic nerve cupping and notching, retinal nerve fiber bundles defect and corresponding visual field loss. Therefore, it was considered that NTG is a subtype of POAG. However, other than the IOP, other significant differences in the clinical signs between NTG and POAG have been noticed.

When compared to those in POAG, the appearance of optic disc in NTG tends to present a narrower neuroretinal rim for a given amount of visual field loss, particularly inferiorly and inferotemporally [25]. Disc hemorrhage and focal LC defects are more often found in NTG [26]. The visual field defects in NTG trend to be closer to fixation, deeper and more focal [27]. These findings suggest that NTG and POAG may be different in their underlying pathophysiology.

Diseases frequently accompanied with NTG, but not POAG

Different from POAG, NTG is usually associated with the vascular failures. The vascular dysregulation appears to be a primary initiating factor for GON in NTG. Ocular blood flow instability affects optic nerve and retina via ischemic damage and promoting the apoptosis of RGCs and damage to axons [15]. Previous studies showed that NTG was associated with a variety of systemic diseases, including migraine, Alzheimer’s disease, primary vascular dysregulation, obstructive sleep apnea-hypopnea syndrome (OSAHS) and Flammer syndrome, and all of these systemic diseases were considered as the risk factors for GON in NTG [17,18]. To our understanding, GON may be a sign of these systemic diseases, or, these diseases may be primary reasons causing abnormal ocular blood supply in patients with GON, as long as the nature of NTG is considered.

(1) Flammer syndrome (primary vascular dysfunction) is characterized by an insufficient or improper adaption of blood flow, despite the presence of anatomically healthy vessels and the absence of a causative disease, and results in a transiently incorrect blood supply for the tissue needs [28]. The patients usually presented with cold hands and/or feet, shifted circadian rhythm, low BP (with pronounced fall during night), and prolonged sleep onset time.

Studies indicated that Flammer syndrome may contribute to the occurrence and progression of NTG. Glaucomatous patients with progressive GON damage often suffered from Flammer syndrome, in spite of whether the IOP is well-controlled or not [29]. Patients with both Flammer syndrome and NTG usually presented with more signs, such as optic disc splinter hemorrhages and diffuse visual field loss. The increased retinal venous pressure and blood flow resistance in the ret- roocular vessels, and increased oxidative stress and activation of retinal astrocytes in Flammer syndrome were also observed [29,30]. Studies also reported that the retinal vessels of the optic nerve head were less shifted to the nasal side in a number of patients with either Flammer syndrome or NTG [31]. Thus, Flammer syndrome induce GON in NTG cases mainly due to low blood pressure, increased retinal venous pressure and improper autoregulation, resulting in ocular blood flow (OBF) instability [15,32].

(2) Migraine is the most well-known vasospastic clinical entity, and a number of investigations reported that the migraine was associated with NTG. Cursiefen et al found that migraine was significantly more
commonly seen in NTG patients than the control subjects and HTG patients [24]. The Collaborative Normal-Tension Glaucoma Study suggested that migraine should be a risk factor for development and progression of NTG [16]. In the Low-Pressure Glaucoma Treatment Study, migraine was thought to be a predicting factor of disc hemorrhage in NTG cases [33].

Corbett et al, using computerized tomographic scan and electroencephalography, showed that 44% of NTG patients had a history of migraine, indicating that migraine-related ischemia might be the pathogenic mechanism in NTG [34]. These results suggest a potential, common vascular etiology of both NTG (or GON) and migraine.

(3) Alzheimer’s disease (AD) is a common type of dementia, characterized by progressive memory deterioration, cognitive dysfunction, abnormal behavior, and other disorders caused by central nervous system degeneration. Retinal vessel abnormalities were detected in NTG and early stage of AD [35]. Retinal vessel signs may reflect the vascular dysregulation in retinal and cerebral microvasculature, leading to low perfusion pressure in patients with glaucoma and AD [35,36]. Sugiyama et al compared regional cerebral blood flow (rCBF) in NTG patients with normal individuals, by using single photon emission computed tomography, found that 22.6% of NTG patients exhibited an AD-like perfusion pattern although none of them was clinically diagnosed as AD. This incidence rate was significantly higher than the rate (1%) of AD reported in a normal population cohort aged 75 or over. Furthermore, the rCBF in the regions of middle cerebral artery perfusion decreased in early stages of AD, while Sugiyama et al also found that the levels of rCBF of these NTG patients were lower in these regions than that in control. All of the above suggest that some of AD patients and NTG patients might share with a common pathogenic mechanism [37].

(4) Systemic hypotension and vasospasm were known as the risk factors for GON. A number of studies have analyzed the relationship between the vasospastic disorders, systemic hypotension and NTG. Low systolic blood pressure was involved in the pathogenesis of disc hemorrhage in NTG [33]. Systemic hypotension, especially nocturnal arterial hypotension, contributes to progression of NTG because of the nerve hypoperfusion. Kim and his colleagues reported that the NTG patients with rapid progression of VF damage and excavation of the optic disc suffered of the low systemic blood pressure in common, with 65% of them suffering of vasospasm [38]. Furthermore, a sustained blood pressure drop during sleep was always observed in these patients [38]. These studies suggested that systemic hypertension plays a role in the onset of disc hemorrhage in NTG, and were the only significant risk factor for disc hemorrhage occurrence in NTG [38]. Therefore, systemic hypotension might be a significant cause for GON.

(5) Obstructive sleep apnea–hypopnea syndrome (OSAHS) is known as a risk factor for glaucoma. There are evidences showing that the prevalence of glaucoma is higher in OSAHS patients, especially in those severe OSAHS with apnea hypopnea index (AHI) > 30, meanwhile the sleep disorders are more frequent in glaucoma patients, especially in NTG [39].

The pathogenesis of GON in OSAHS cases with NTG were hypothesized to be related to recurrent hypoxia with increased vascular resistance, autonomic deregulation, oxidative stress and inflammation linked to hypoxia and subsequent reperfusion, decreased cerebral perfusion pressure and direct hypoxic damage to the optic nerve [39]. Thus, treatment with continuous positive airway pressure may contribute to prevention of GON from progression [39].

(6) Abnormal vasoregulation, such as Raynaud’s phenomenon, is more associated with NTG than POAG. Raynaud phenomenon is an exaggerated physiological response of the extremities to exposure to cold or emotional stress, etc.

Studies showed that Raynaud’s phenomenon is the clinical manifestation of a generalized vasospastic disorder, which is especially supported in patients who have Prinzmetal’s angina, migraine or scleroderma [40].

Although the exact pathophysiology of Raynaud’s phenomenon has not been understood yet, there is consensus that vasospastic mechanisms are involved in its pathogenesis. At least fifty etiological theories have been postulated, most of them concerning dysregulation of the neuroendothelial control of vascular tone caused by imbalance between vasoconstrictive and vasodilating mediators [41].

(7) There is growing clinical evidence to support the hypothesis that intracranial hypertension may play an important role in GON and glaucomatous retinopathy. The Beijing intracranial and intraocular pressure (ICOP) reported a positive association between TLPD (translaminia cribrosa pressure difference) and visual field defects in POAG patients [42]. A population-based study from the Korean National Health and Nutrition Examination Survey (KNHANES) found that TLPD was significantly associated with NTG [43].

Two mechanisms have been proposed to describe the influence of intracranial hypertension on glaucoma pathology. The first of which suggests that a lower intracranial pressure leads to similar mechanical deformation of the ONH as has previously been reported for higher IOP [44]. This hypothesis is contested on grounds including that the rigid structure of the LC will resist bowing at TLPDs of clinically relevant magnitude [45]. The second mechanism is that the dysregulation of cerebral spinal fluid (CSF) hydrodynamics, manifesting as elevated CSF pressure and resulting in accumulation of toxic compounds at the site of the ONH, leads to RGC loss [46].

Those disorders are previously considered as risk factors for both POAG and NTG. For the former it appears to be correct, but for the latter, these disorders seem to be likely the causative factors rather than risk factors. As discussed, it is probably more accurate to state that GON is one of the signs, or a part, of these primary diseases. In another word, GON, as so called, is not specifically seen in glaucoma, instead, is a result of a number of diseases in which the vascular dysregulation and vasoconstriction are actively involved in their pathogenesis.

What are the mechanisms underlying the Bjerrum scotoma?

It is known that the glaucomatous defect represents the damages to the nerve fiber bundle. The characteristic glaucomatous visual field loss includes nasal step, seidel scotoma and arcuate scotoma (or Bjerrum scotoma), seen in patients with glaucoma. Bjerrum scotoma occurs in the area 10–20 degrees from fixation, indicating damage to the corresponding nerve fiber bundles in the retina. The question is whether this type of damage is only specifically seen in glaucoma (e.g. elevated IOP) or it can also be observed in other injuries such as vasospasm and ischemia.

In both POAG and NTG, vascular dysfunction in the optic nerve head (ONH), induced by compression or vasospasm, respectively, has been considered as a possible mechanism in the pathogenesis of GON. No matter what mechanism is present, the reduced perfusion pressure and reduction of ocular blood flow to ONH cause ischemic damage to the optic nerve [17]. Radial peripapillary capillaries (RPCs) likely originate from intraretinal peripapillary arterioles and are most prominent in an area extending infero- and supero-temporally (4 mm to 5 mm) from the optic nerve absent in the central macular region, forming an arcuate configuration and nourishing the surrounding retinal nerve fiber bundles [47,48]. It was suggested that, for two reasons, preferential or selective involvement of the RPCs occurs in states of elevated IOP or in hemodynamic disorders. First, since their longer path length, RPCs may encounter greater resistance to blood flow than that in the rest of the retinal capillary network. Second, the RPCs derive from single small peripapillary arterioles and they have few vascular anastomoses with adjacent capillaries. Therefore, the vasoconstrictive and environmental insults including elevated IOP may probably influence first the flow in the RPCs.

Based on their pattern and distribution, the RPCs were inferred to supply the peripapillary superficial nerve fiber layer. Previous studies postulated the underfilling of RPCs could cause the corresponding RNFL...
loss, which manifests clinically as Bjerrum scotoma in glaucoma pa-
tients. The hypothesis was supported by an experimental study on cat
eyes, after experimentally induced IOP elevation, Indian pink dye
perfusion showed selective underfilling of the RPCs [49]. If these RPCs
are indeed compromised by an elevated IOP in glaucoma patients, the
clinical reflection of the physiological abnormality would be arcuate
Bjerrum scotoma.

A histological study of 15 postmortem eyes from 10 glaucoma pa-
tients, found that the RPCs presented atrophic changes in glaucomatous
eyes [50]. The authors hypothesized that the characteristics of RPCs
made them more vulnerable to elevated IOP in glaucoma, and event-
tually become atrophic, leading to ischemia and dysfunction of the
 Corresponding author.

should the term “normal tension glaucoma” be ignored?

It is generally accepted that GON is characterized by progressive
retinal ganglion cell loss and visual field defects. GON in POAG is
mainly a result of elevated IOP, but the reasons for the abnormal IOP
are still unknown. Whilst GON in NTG is caused mainly by reduced
ocular blood flow (OBF) instead of IOP [17,18]. The question then
arises: Is “normal tension glaucoma” truly glaucoma? As discussed
above, GON induced by elevated IOP is called POAG. If the GON is not
called POAG. If the GON is not caused by IOP, instead, it caused by reduced OBF or other IOP-in-
dependent factors, it is not glaucoma. Actually, GON by nature can not

represent a distinct disease entity, it is just a sign, which is shared by a
number of disease entities, including, but not limited to, POAG.

The term “glaucomatous” optic neuropathy (GON) describes an
optic neuropathy which was used to be considered as a typical phe-
notype of POAG. Increasing evidences showed that there are a number
of disorders can present with “GON” as a sign. Therefore, “GON” is a
very confusing concept, and that is one of the major reasons for this
hypothesis. In summary, “GON”, to the best of our understanding, is an
incorrect term, and should be corrected.

Therefore, NTG is frequently secondary to systemic disorders in-
cluding Flammer syndrome, migraine, systemic hypotension, OSAHS,
avascular abnormalities, vasospasm, Alzheimer’s disease and intracranial hypotension.

ったfig. 2. The diseases likely capable of causing GON. GON is a phenotype of a
number of diseases which can cause the characterized optic neuropathy, in-
cluding POAG with elevated IOP (HTG) and other systemic disorders like
Flammer syndrome, migraine, systemic hypotension, OSAHS, abnormal vasor-
egulation, vasospasm, Alzheimer’s disease and intracranial hypotension.

Fig. 1. Optical coherence tomography angiography (OCTA) vessel density image of radial peripapillary capillaries (RPCs, Panel A), and the scanning laser oph-
thalmoscopy (SLO) fundus image of the scan area (Panel B). The RPCs follow a very similar trajectory to the RGC axons in the NFL with minimal anastomoses.
Even though the increasing evidences suggest that compromised tissue blood flow in the ONH is also actively involved in formation of GON, the mainstream treatment for both POAG and NTG is IOP reduction. For the latter, based on the Collaborative Normal-Tension Glaucoma Study, a 30% IOP reduction favorably influenced the progression of this disease in glaucoma patients compared with untreated NTG controls [16,55]. It was then thought that it is not necessary to change or ignore the term NTG since the management remains the same. However, the following should be taken into consideration.

(1) The benefit of IOP reduction for NTG patients may be quite uncertain. Despite the low IOP after treatment, approximately 50% of patients with NTG had VF defect progression as detected by perimetry [56,57]. Collaborative Normal Tension Glaucoma Study (CNTGS) compared treatment versus no treatment in NTG. No correlation with IOP levels maintained during follow up was found between the two groups, and no benefit of treatment was found in the intent-to-treat analysis either [16]. Recently, the Low-Pressure Glaucoma Treatment Study (LoGTS) has raised questions about the choice of drug therapy in NTG. The results suggest the possibility that brimonidine is neuroprotective and timolol is neurodestructive when used as monotherapy for NTG [58]. In other words, brimonidine may exert its effects on NTG via its effect of improving vascular circulation in retina instead of its effects on IOP, and beta blockers may even have a deleterious effect in NTG.

(2) Certain anti-glaucoma medications may exert their effects due to IOP-independent pathways. Reducing IOP may improve the blood supply to optic nerve. Therefore, the administration of IOP lowering medication may exert its effects by improving blood circulation instead of lowering IOP. If this is true, performing ocular massage to lower IOP may also be useful.

(3) Additional effects of antiglaucoma drugs on ONH blood flow should have important clinical implications and significance. Evaluation of the effects of the nonselective β-adrenergic antagonists on tissue blood flow in the ipsilateral ONH both in glaucoma patients and normal volunteers, which cannot be attributed to its IOP reducing effect [60–62].

(4) Treatment targeting the primary disorders associated NTG appears effective to patients with NTG. Furthermore, treatments targeting the primary disorders associated NTG appears effective to patients with NTG. Several studies revealed that differences between NTG and high-pressure POAG, and IOP appears not to be the key issue to differentiate these two disorders, even for the treatment as described above. POAG is due to the elevated IOP but NTG is not, instead, it is due to other mechanisms other than IOP. If the primary diseases causing GON can be identified, the patients with NTG are then misdiagnosed. The term of either NTG or GON obviously causes confusions. Future treatment of NTG should target the primary disorders responsible for occurrence of GON.

In conclusion, NTG shares similar clinical manifestations and disease progression with POAG, but represents different and non-glaucomatous entities. POAG is primary disease with unknown pathogenesis, but NTG, at least for some of the cases, is not. The characteristic optic disc cupping and visual field defect including typical arcuate Bjerrum scotoma is not only generated by glaucoma. For those secondary to one or more known disease, NTG (or GON) may just be one of the phenotypes. In another word, NTG is different from POAG and caused by a number of disorders and affected by IOP-independent risk factors. Therefore, if NTG is still considered as a subtype or special form of POAG, it will cause confusions for diagnosis and management, and misunderstanding, of glaucoma. In order to distinguish GON among the various conditions, it is crucial to define glaucoma based on disease causing factors like IOP instead of the phenotypes like the characteristic changes in the optic nerve. Furthermore, clinical trials and/or multiple center studies to further differentiate NTG from IOP-related glaucoma are essentially needed.

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### Declaration of Competing Interest

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