Is "normal tension glaucoma" glaucoma?

Ning Fan[a], Junkai Tan[b], Xuyang Liu[b],*

[a] *Shenzhen Eye Hospital, School of Optometry, Shenzhen University, China*
[b] *Xiamen Eye Center, Xiamen University, China*

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 [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 [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 [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 [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 [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 [15]. Up to date, there is no evidence showing that the normal IOP is

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harmful to eyes with NTG or GON.

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 recognition 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 glaucomatous and contralateral nonglaucomatous eyes [23].

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 inferotemporal [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 despite 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 retrocular 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 hypotension may play an important role in GON and glaucomatous retinopathy. The Beijing intracranial and intraocular pressure (iCOP) reported a positive association between TLPD (translamina 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 hypotension 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 CSFP 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 patients. 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 patients, 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 eventually become atrophic, leading to ischemia and dysfunction of the corresponding retinal nerve fibers as clinically manifested as Bjerrum scotoma [50].

Thus, the RPCs are radically distributed around the optic disc, and had a double Bjerrum archlike configuration [51]. The function of RPCs is to supply and nourish the inner portion of the RNFL. The unique pattern and distribution of these vessels make them vulnerable to compressive or vasoconstrictive factors including elevated IOP and vasospasm compared with other retinal capillaries, and the selective damages thus manifest clinically as Bjerrum scotoma.

The application of optical coherence tomography angiography (OCT-A) makes it feasible to image and direct visualization the RPCs network in vivo (Fig. 1). Mansoori et al observed focal loss of RPCs in patients with early POAG, compared with normal controls [47]. Mammo et al reported that a significant reduction in RPC density was correlated with sites of NFL thinning and Bjerrum scotoma-like visual field loss in glaucoma [52].

Taking together, Bjerrum scotoma, together with its corresponding GON, is not particularly only observed in POAG and NTG, instead, it can be seen in a number of disorders including elevated IOP, vascular dysfunction and ischemia, etc. In another word, GON is not a sign specifically for POAG, instead, it seems to be a result of many disorders capable of affecting radial peripapillary capillaries of the retina, and in VF, it can be plotted as typical arcuate Bjerrum scotoma.

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 caused by IOP, instead, it caused by reduced OBF or other IOP-independent factors, it is not glaucoma. Actually, GON by nature can not

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, including POAG with elevated IOP (HTG) and other systemic disorders like Flammer syndrome, migraine, systemic hypotension, OSAHS, abnormal vasoregulation, vasospasm, Alzheimer's disease and intracranial hypotension.

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 phenotype 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 including Flammer syndrome, migraine, systemic hypotension, OSAHS, abnormal vasoregulation, vasospasm, Alzheimer's disease and intracranial hypotension [53,54]. Different from NTG, POAG cannot be diagnosed if the IOP is not elevated, even though it can be influenced by risk factors as seen in NTG (Fig. 2).
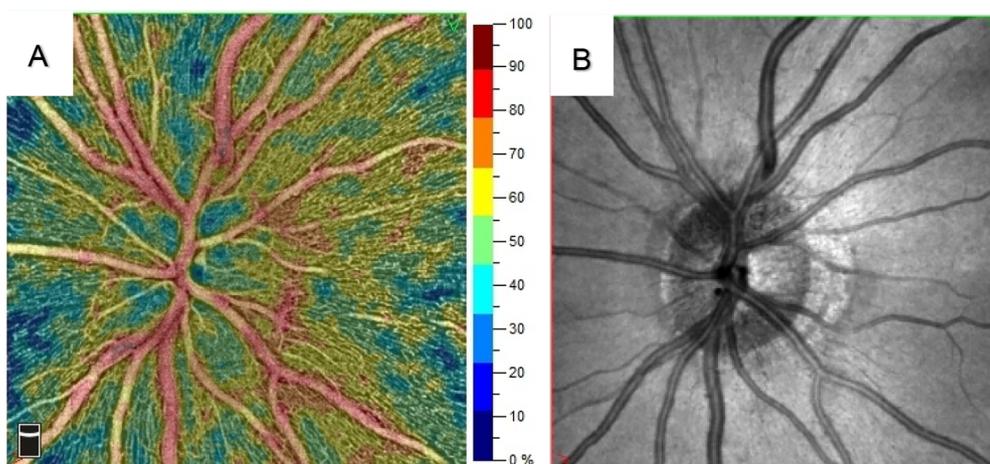

Fig. 1. Optical coherence tomography angiography (OCTA) vessel density image of radial peripapillary capillaries (RPCs, Panel A), and the scanning laser ophthalmoscopy (SLO) fundus image of the scan area (Panel B). The RPCs follow a very similar trajectory to the RGC axons in the NFL with minimal anastomoses.

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 human ONH circulation suggested a beneficial influence of long-term carteolol or betaxolol therapy on the ONH circulation [59]. Recent studies indicated that the topical FP-receptor agonists, tafluprost or latanoprost, are able to significantly increase the blood velocity and 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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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Vranka Janice A, Acott Ted S. Pressure-induced expression changes in segmental flow regions of the human trabecular meshwork. Exp Eye Res 2017;158:67–72.

[2] Oh Dong-Jin, Kang Min Hyung, Ooi Yen Hoong, Choi Kyu Ryong, Helene Sage E, Rhee Douglas J. Overexpression of SPARC in human trabecular meshwork increases intraocular pressure and alters extracellular matrix. Invest Ophthalmol Vis Sci 2013;54(5):3309–19.

[3] Rocha-Sousa A, Rodrigues-Araújo J, Gouveia Petra, Barbosa-Breda João, Azevedo-Pinto S, Pereira-Silva P, et al. New therapeutic targets for intraocular pressure lowering. ISRN Ophthalmol 2013;2013:261386.

[4] Menaa Farid, Braghini Carolina Ayumi, De Vasconcellos Jose Paulo Cabral, Menaa Bouzid, Costa Vital Paulino, De Figueiredo Eugênio Santana, et al. Keeping an eye on myocilin: a complex molecule associated with primary open-angle glaucoma susceptibility. Molecules 2011;16(7):5402–21.

[5] Jain Ankur, Zode Gulab, Kasetti Ramesh B, Ran Fei A, Yan Winston, Sharma Tasneem P, et al. CRISPR-Cas9-based treatment of myocilin-associated glaucoma. Proc Natl Acad Sci. 2017;114(42):11199–204.

[6] Burr JM, Mowatt G, Hernandez R, et al. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. Health Technol Assess 2007;11(41). iii-iv, ix-x, 1-190.

[7] Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol 2002;120(10):1268–79.

[8] Bermudez Jaclyn Y, Montecchi-Palmer Michela, Mao Weiming, Clark Abbot F. Cross-linked actin networks (CLANs) in glaucoma. Exp Eye Res 2017;159:16–22.

[9] Wallace Deborah M, Murphy-Ullrich Joanne E, Crawford Downs J, O'Brien Colm J. The role of matricellular proteins in glaucoma. Matrix Biol 2014;37:174–82.

[10] Agapova OA, Ricard CS, Salvador-Silva M, Hernandez MR. Expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases in human optic nerve head astrocytes. Glia 2001;33(3):205–16.

[11] Burgoyne Claude F, Crawford Downs J, Bellezza Anthony J, Francis Suh J-K, Hart Richard T. The optic nerve head as a biomechanical structure: a new paradigm for understanding the role of IOP-related stress and strain in the pathophysiology of glaucomatous optic nerve head damage. Prog Retin Eye Res 2005;24(1):39–73.

[12] Yang Hongli, Thompson Hilary, Roberts Michael D, Sigal Ian A, Crawford Downs J, Burgoyne Claude F. Deformation of the early glaucomatous monkey optic nerve head connective tissue after acute IOP elevation in 3-D histomorphometric reconstructions. Invest Ophthalmol Vis Sci 2011;52(1):345–63.

[13] Fiona McDonnell W, Dismuke Michael, Overby Darryl R, Daniel Stamer W. Pharmacological regulation of outflow resistance distal to Schlemm's canal. Am J Physiol Cell Physiol 2018;315(1):C44–51.

[14] Tsai James C, Kanner Elliott M. Current and emerging medical therapies for glaucoma. Expert Opin Emerg Drugs 2005;10(1):109–18.

[15] Trivli Alexandra, Koliarakis Ioannis, Terzidou Chryssa, Goulielmos George N, Siganos Charalambos S, et al. Normal-tension glaucoma: Pathogenesis and genetics. Exp Ther Med 2019;17(1):563–74.

[16] Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol 1998;126(4):498–505.

[17] Fan Ning, Wang Pei, Tang Li, Liu Xuyang. Ocular blood flow and normal tension glaucoma. Biomed Res Int 2015;2015:308505.

[18] Nakazawa Toru. Ocular blood flow and influencing factors for glaucoma. Asia Pac J Ophthalmol (Phila) 2016;5(1):38–44.

[19] Dias DT, Ushida M, Battistella R, Dorairaj S, Prata TS. Neurophthalmological conditions mimicking glaucomatous optic neuropathy: analysis of the most common causes of misdiagnosis. BMC Ophthalmol 2017;17(1):2.

[20] Kim Jee Hyun, Lee Tae Yoon, Lee Jong Wook, Lee Kyoo Won. Comparison of the thickness of the lamina cribrosa and vascular factors in early normal-tension glaucoma with low and high intraocular pressures. Korean J Ophthalmol 2014;28(6):473–8.

[21] Yamamoto Shunichi, Sawaguchi Shoichi, Iwase Aiko, Yamamoto Tetsuya, Abe Haruki, Tomita Goji, et al. Primary open-angle glaucoma in a population associated with high prevalence of primary angle-closure glaucoma: the Kumejima Study. Ophthalmology 2014;121(8):1558–65.

[22] Kim Ji Hyun, Kang Sung Yong, Kim Na Rae, Lee Eun Suk, Hong Samin, Seong Gong Je, et al. Prevalence and characteristics of glaucoma among Korean adults. Korean J Ophthalmol 2011;25(2):110–5.

[23] Wang NL, Friedman DS, Zhou Q, Guo L, Zhu D, Peng Y, et al. A population-based assessment of 24-hour intraocular pressure among subjects with primary open-angle glaucoma: the handan eye study. Invest Ophthalmol Vis Sci 2011;52(11):7817–21.

[24] Cursiefen C, Wisse M, Cursiefen S, Jünemann A, Martus P, Korth M. Migraine and tension headache in high-pressure and normal-pressure glaucoma. Am J Ophthalmol 2000;129(1):102–4.

[25] Caprioli J, Spaeth GL. Comparison of the optic nerve head in high- and low-tension glaucoma. Arch Ophthalmol 1985;103(8):1145–9.

[26] Pruzan Noelle L, Myers Jonathan S. Phenotypic differences in normal vs high tension glaucoma. J Neuroophthalmol. 2015;35(Suppl. 1):S4–7.

[27] Song Brian J, Caprioli Joseph. New directions in the treatment of normal tension glaucoma. Indian J Ophthalmol 2014;62(5):529–37.

[28] Mozaffarieh Maneli, Flammer Josef. New insights in the pathogenesis and treatment of normal tension glaucoma. Curr Opin Pharmacol 2013;13(1):43–9.

[29] Konieczka Katarzyna, Ritch Robert, Traverso Carlo Enrico, Kim Dong Myung, Kook Michael Scott, Gallino Augusto, et al. Flammer syndrome. EPMA J 2014;5(1):11.

[30] Flammer Josef, Konieczka Katarzyna, Flammer Andreas J. The primary vascular dysregulation syndrome: implications for eye diseases. EPMA J 2013;4(1):14.

[31] Konieczka K, Fränkl S, Todorova MG, Henrich PB. Unstable oxygen supply and glaucoma. Klin Monbl Augenheilkd 2014;231(2):121–6.

[32] Gherghel D, Orgül S, Gugleta K, Flammer J. Retrobulbar blood flow in glaucoma patients with nocturnal over-dipping in systemic blood pressure. Am J Ophthalmol 2001;132(5):641–647f.

[33] Furlanetto Rafael L, De Moraes Carlos Gustavo, Teng Christopher C, Liebmann Jeffrey M, Greenfield David S, Gardiner Stuart K, et al. Risk factors for optic disc hemorrhage in the low-pressure glaucoma treatment study. Am J Ophthalmol 2014;157(5):945–52.

[34] Corbett JJ, Phelps CD, Eslinger P, Montague PR. The neurologic evaluation of patients with low-tension glaucoma. Invest Ophthalmol Vis Sci 1985;26(8):1101–4.

[35] de la Torre JC. Alzheimer disease as a vascular disorder: nosological evidence. Stroke 2002;33(4):1152–62.

[36] Tian Tian, Liu Yun-Hai. Normal-tension glaucoma and Alzheimer's disease: retinal vessel signs as a possible common underlying risk factor. Med Hypotheses 2011;77(3):466.

[37] Sugiyama Tetsuya, Utsunomiya Keita, Ota Hitoya, Ogura Yasuharu, Narabayashi Isamu, Ikeda Tsunehiko. Comparative study of cerebral blood flow in patients with normal-tension glaucoma and control subjects. Am J Ophthalmol 2006;141(2):394–6.

[38] Kim Y-D, Han SB, Park KH, Kim SH, Kim SJ, Seong M, et al. Risk factors associated with optic disc haemorrhage in patients with normal tension glaucoma. Eye (Lond) 2010;24(4):567–72.

[39] Pérez-Rico Consuelo, Gutiérrez-Díaz Esperanza, Mencía-Gutiérrez Enrique, Díaz-de-Atauri María Josefa, Blanco Román. Obstructive sleep apnea-hypopnea syndrome (OSAHS) and glaucomatous optic neuropathy. Graefes Arch Clin Exp Ophthalmol 2014;252(9):1345–57.

[40] Wigley Fredrick M. Raynaud's phenomenon. N Engl J Med 2002;347(13):1001–8.

[41] Terwindt GM, Haan J, Ophoff RA, Groenen SM, Storimans CW, Lanser JB, et al. Clinical and genetic analysis of a large Dutch family with autosomal dominant vascular retinopathy, migraine and Raynaud's phenomenon. Brain 1998;121(Pt 2):303–16.

[42] Hou R, Zhang Z, Yang D, Wang H, Chen W, Li Z, et al. Pressure balance and imbalance in the optic nerve chamber: the Beijing Intracranial and Intraocular Pressure (iCOP) Study. Sci China Life Sci 2016;59(5):495–503.

[43] Lee SH, Kwak SW, Kang EM, Kim GA, Lee SY, Bae HW, et al. Estimated trans-lamina cribrosa pressure differences in low-teen and high-teen intraocular pressure normal

[44] Jonas JB, Berenshtein E, Holbach L. Anatomic relationship between lamina cribrosa, intraocular space, and cerebrospinal fluid space. Invest Ophthalmol Vis Sci 2003;44(12):5189–95.

[45] Hayreh SS. Cerebrospinal fluid pressure and glaucomatous optic disc cupping. Graefe's Arch Clin Exp Ophthalmol 2009;247(6):721–4.

[46] Wostyn P, Van Dam D, Audenaert K, Killer HE, De Deyn PP, De Groot V. A new glaucoma hypothesis: a role of glymphatic system dysfunction. Fluids Barriers CNS 2015;12:16.

[47] Mansoori Tarannum, Sivaswamy Jayanthi, Gamalapati Jahnavi Sai, Balakrishna Nagalla. Radial peripapillary capillary density measurement using optical coherence tomography angiography in early glaucoma. J Glaucoma 2017;26(5):438–43.

[48] Henkind P. Radial peripapillary capillaries of the retina. I. Anatomy: human and comparative. Br J Ophthalmol. 1967;51(2):115–23.

[49] Alterman M, Henkind P. Radial peripapillary capillaries of the retina. II. Possible role in Bjerrum scotoma. Br J Ophthalmol 1968;52(1):26–31.

[50] Kornzweig AL, Eliasoph I, Feldstein M. Selective atrophy of the radial peripapillary capillaries in chronic glaucoma. Arch Ophthalmol 1968;80(6):696–702.

[51] Henkind P. Symposium on glaucoma: joint meeting with the National Society for the Prevention of Blindness. New observations on the radial peripapillary capillaries. Invest Ophthalmol 1967;6(2):103–8.

[52] Mammo Zaid, Heisler Morgan, Balaratnasingam Chandrakumar, Lee Sieun, Yu Dao-Yi, Mackenzie Paul, et al. Quantitative optical coherence tomography angiography of radial peripapillary capillaries in glaucoma, glaucoma suspect, and normal eyes. Am J Ophthalmol 2016;170:41–9.

[53] Zaleska-Żmijewska Anna, Janiszewski Maciej, Wawrzyniak Zbigniew M, Kuch Marek, Szaflik Jerzy, Szaflik Jacek P. Is atrial fibrillation a risk factor for normal-tension glaucoma? Medicine (Baltimore) 2017;96(43). e8347.

[54] Mudumbai Raghu C. Clinical update on normal tension glaucoma. Semin Ophthalmol 2013;28(3):173–9.

[55] Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol 1998;126(4):487–97.

[56] Kim M, Kim DM, Park KH, Kim TW, Jeoung JW, Kim SH. Intraocular pressure reduction with topical medications and progression of normal-tension glaucoma: a 12-year mean follow-up study. Acta Ophthalmol 2013;91(4):e270–5.

[57] Komori S, Ishida K, Yamamoto T. Results of long-term monitoring of normal-tension glaucoma patients receiving medical therapy: results of an 18-year follow-up. Graefes Arch Clin Exp Ophthalmol 2014;252(12):1963–70.

[58] Krupin T, Liebmann JM, Greenfield DS, Ritch R, Gardiner S, Low-Pressure Glaucoma Study Group. A randomized trial of brimonidine versus timolol in preserving visual function: results from the Low-Pressure Glaucoma Treatment Study. Am J Ophthalmol 2011;151(4):671–81.

[59] Tamaki Y, Araie M, Tomita K, Nagahara M. Effect of topical betaxolol on tissue circulation in the human optic nerve head. J Ocul Pharmacol Ther 1999;15(4):313–21.

[60] Tsuda Satoru, Yokoyama Yu, Chiba Naoki, Aizawa Naoko, Shiga Yukihiro, Yasuda Masayuki, et al. Effect of topical tafluprost on optic nerve head blood flow in patients with myopic disc type. J Glaucoma 2013;22(5):398–403.

[61] Ishii K, Tomidokoro A, Nagahara M, Tamaki Y, Kanno M, Fukaya Y, et al. Effects of topical latanoprost on optic nerve head circulation in rabbits, monkeys, and humans. Invest Ophthalmol Vis Sci 2001;42(12):2957–63.

[62] Tamaki Y, Nagahara M, Araie M, Tomita K, Sandoh S, Tomidokoro A. Topical latanoprost and optic nerve head and retinal circulation in humans. J Ocul Pharmacol Ther 2001;17(5):403–11.