Review Article

Normal tension glaucoma: Prevalence, etiology and treatment

George Ayoub¹,²*, Yanan Luo³ and Dominic Man-Kit Lam¹

¹World Eye Organization, 1209 Shui on Centre, 6 Harbour Road, Hong Kong
²Department of Psychology, University of California, Santa Barbara, CA, 93106, USA
³College of Chemistry, Central China Normal University, Wuhan, 430079 PRC, China

Abstract

Normal tension glaucoma is the most common type of glaucoma among people of east Asian countries. While a significant minority of cases of normal tension glaucoma respond to drugs or surgical procedures that lower intra-ocular pressure, most cases continue to progress, resulting in a continuing loss of visual field and blindness. We here review the current state of knowledge of this debilitating disease, and evaluate a promising pilot study showing a potential route to evaluate normal tension glaucoma and to effectively treat it with a vitamin and mineral supplement.

Introduction

Glaucoma is a visual disorder that is increasing in prevalence. While most cases of glaucoma world-wide present with an increased pressure in the eye, the majority of cases of open-angle glaucoma in China, Japan and Korea have normal intraocular pressure (IOP) and are called normal tension glaucoma (NTG). Clinical evaluation indicates that abnormal retinal blood flow is a feature of any glaucoma but in particular of NTG, a condition with few treatment options, and one that results in glaucomatous optic neuropathy (GON) and diminished visual field.

Recent evidence has identified that while IOP is normal in NTG, measurement of retinal venous pressure (RVP) reveals often elevated levels. Current treatment for NTG is limited to reduction in IOP, which is marginally effective. RVP increases are often associated with disturbed microcirculation, due to limited autoregulation and altered endothelial cells related e.g. to Flammer syndrome. A reduction of GON from NTG in response to vitamin supplementation to restore normal RVP, as detailed in this review, will provide a powerful tool to curtail progression of NTG. Additionally, using RVP measurement as a biomarker for NTG provides an early diagnostic for this debilitating disease.

A three month pilot study with glaucoma patients that directly tested this hypothesis has proven effective in identifying NTG and presumed NTG by the presence of elevated RVP. Treatment of patients with Ocufolin forte was effective in reducing RVP as well as elevated homocysteine levels, a biomarker for deficiencies. Ocufolin contains micronutrients and is well tolerated, with no reported adverse implications. We suggest RVP screening of those at risk for NTG and treatment of elevated RVP with Ocufolin forte as a viable diagnosis and treatment for this common type of glaucoma.

Epidemiology

Globally, glaucoma impacts over 70 million people with one in ten bilaterally blind, making it the leading cause of irreversible blindness. Glaucoma is often asymptomatic prior to vision reduction, so those afflicted is likely much greater than reported numbers [1]. Worldwide, all types of glaucoma account for 6.5% of blindness, and the prevalence of glaucoma of all types is 3.5% for people over 40 years [2]. Tham, et al. [3] projected an increase of 50% of all types of glaucoma in the next two decades.

The global prevalence of all types of glaucoma is detailed by Chen et al [4], Tham, et al. [3] and Kim, et al. [5]. Within Asian populations, normal tension glaucoma (NTG) comprises 70%
of primary open angle glaucoma (POAG), with values 75-90% in China, Singapore, Japan and Korea, and 50–70% in India and Nepal [5]. Diagnosis of NTG is determined from the presence of POAG signs such as damage to the optic nerve head in the presence of normal Intraocular Pressure (IOP). The standard treatment of NTG is to lower IOP, control systemic risk factors and improve ocular perfusion.

High tension glaucoma predominates in people with origins in Africa and Europe, while NTG predominates in people with origins in east Asia. In the Wang, et al. [6] consensus report on NTG in China, which draws from the major medical centers in China, they identified NTG afflicting 1% of the Chinese population, and that NTG comprises 70% of POAG cases. They report that in healthy populations, the average IOP is 17 for white people and 15 for Chinese, while POAG averaged 22 [6]. They found that patients meeting the characteristics of Flammer Syndrome (FS) have a lower intracranial pressure, leading to an increased gradient at the lamina cribosa, and a resultant decrease in perfusion of the optic nerve. Wang, et al. [6] provide guidance for treatment of NTG based on patient specifics.

Flammer syndrome, which is often associated with NTG, describes a phenotype of people having a predisposition for an altered vascular reaction to stimuli such as cold, emotional stress or high altitude. Common symptoms are: cold extremities, low blood pressure, prolonged sleep onset time, reduced feeling of thirst, increased sensitivity to odor, pain, vibration and certain drugs. FS subjects are often ambitious, successful, perfectionists and sometimes brooding. Frequent signs are: altered gene expression, prolonged blood flow cessation in nailfold capillaroscopy after cold provocation, reduced autoregulation of ocular blood flow and reduced retinal vasodilation after stimulation with flickering light. Retinal venous pressure is on average higher and retinal astrocytes are more often activated. FS occurs more often in females than in males, in thin than in obese subjects, in young than in old people, in graduates than in blue collar workers, in subjects with indoor than outdoor jobs [7]. Associated diseases are: normal tension glaucoma, occlusion of ocular vessels, retinitis pigmentosa, multiple sclerosis, tinnitus or even sudden hearing loss.

**Etiology**

NTG, alternately termed low tension glaucoma or normal pressure glaucoma, manifests with optic disc flame hemorrhages and cupping, while IOP remains under 21 mmHg [8,9]. While NTG is generally considered to be similar to POAG in the outcomes, its etiology is different, and the mechanism of damage is different from POAG with high IOP [10].

Current thinking on NTG is that damage to the retina may be due to a lack of perfusion, with reports of disrupted ocular blood flow (OBF) [11] possibly due to an increase in retinal venous pressure (RVP) causing damage to the axons of the retinal ganglion cells that comprise the optic nerve [1].

Trivili et al. [9] reviewed NTG pathogenesis, and developed a model (Figure 1) showing that an increase in RVP causes a decrease in OBF, which impacts the Retinal Ganglion Cells (RGC), resulting in a change in the Optic Nerve Head (ONH). The work of Fan et al [14, 15] showed that NTG has a disturbed OBF as measured with imaging techniques, and NTG is comorbid with systemic disorders, including migraine, hypotension, Alzheimer’s disease and Flammer Syndrome [7,16]. Fan, et al. [15] suggest that NTG may not be glaucoma, but a group of disorders with GON. This has implications for what may be best practice in treatment.

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often associated vein occlusions can be a consequence of local vein dysregulation [19].

Gugleta [20] described the significance of endothelin-1 (ET-1) in glaucoma. Endothelin-1 is vasoconstrictive and is a ubiquitous molecule that occurs in nearly all tissues. Its primary physiological function is regulation of blood vessel diameter and thus the regulation of blood supply in tissues. It is secreted locally and exerts its effects locally. Endothelin-1 is involved in the regulation of blood flow in the retina and the optic nerve [12].

Flammer and Konieczka [16] evaluated the role of endothelin on retinal venous pressure (RVP). In healthy subjects RVP is usually equal to or slightly above intraocular pressure (IOP), while RVP is often significantly increased in patients with eye or systemic disease.

This indicates endothelin-1 is a useful biomarker for RVP, with another important biomarker being homocysteine.

Homocysteine levels and the frequency of heterozygous methylenetetrahydrofolate reductase (MTHFR) C677T mutation are increased in open-angle glaucoma. Since homocysteine can induce vascular injury, alterations in extracellular matrix remodeling, and neuronal cell death, these findings may have important implications for understanding glaucomatous optic neuropathy [21].

In the comprehensive review of homocysteine as a biomarker by Smith and Refsum [22], they find 100 diseases or conditions that are associated with raised concentrations of plasma homocysteine. The commonest associations are with cardiovascular diseases and diseases of the central nervous system, but a large number of developmental and age-related conditions are also associated. Few disease biomarkers have so many associations. The clinical importance of homocysteine as a biomarker becomes apparent if lowering plasma homocysteine by B vitamin treatment can reduce disease. Smith and Refsum [22] reported five diseases that are diminished by lowering total homocysteine: neural tube defects, impaired childhood cognition, macular degeneration, primary stroke, and cognitive impairment in the elderly. They concluded that plasma homocysteine levels in adults of 10 μmol/L or less are probably safe, but that values of 11 μmol/L or above may justify intervention. Homocysteine is more than a disease biomarker: it may be a useful guide for the prevention of disease [22,23].

The data in Schmidl [24] showed that a three-month intake of a dietary supplement containing L-methylfolate can significantly reduce blood homocysteine levels in patients with diabetes. This is of importance because higher plasma levels of homocysteine are linked with an increased risk of vascular associated systemic diseases and eye diseases. The review of such nutritional therapies for treatment of diabetic retinopathy by Shi et al [25] gives the additional explanation of the utility of each component in the dietary supplement. Whether systemic L-methylfolate supplementation affects retinal perfusion must be studied in a larger population, but the utility of a single vitamin/mineral supplement to address nutritional deficiencies in retinal vasculature would be a logical extension of treatments supported by the Age–Related Eye Disease Studies (AREDS) [25].

Homocysteine (Hcy) and endothelin-1 are useful biomarkers for elevated retinal venous pressure. As seen in Devogelaere [26] Hcy is elevated in NTG and other types of glaucoma. Efficient reduction of Hcy with vitamin supplementation was already shown by Schmidl [24].

Retinal venous pressure (RVP) may be measured non-invasively by ophthalmodinamometry [27,28]. While RVP is equal to or slightly above IOP in healthy people, it is often increased in patients with eye or systemic diseases. Beyond mechanical obstruction, the main cause of such elevation is a local dysregulation of a retinal vein, typically a constriction induced by endothelin-1 (ET-1, Figure 1). Local increase of ET-1 can be due to a higher blood level, as ET-1 can diffuse from the fenestrated capillaries of the choroid into the optic nerve head (ONH), bypassing the blood retinal barrier. A local increase can also result from increased local production either by a diseased retinal artery or retinal tissue. Generally, the main factors increasing ET-1 are inflammation and hypoxia. RVP is known to be increased in patients with glaucoma, retinal vein occlusion, diabetic retinopathy, high mountain disease, and primary vascular dysregulation (PVD). PVD is the major vascular component of Flammer Syndrome (FS). The increase in RVP decreases perfusion pressure, which increases the risk of hypoxia and ischemia. An increase of RVP also raises transmural pressure, which in turn raises the risk for retinal edema. In patients with retinal vein occlusion, elevated RVP may be both a consequence and a potential cause of the occlusion, causing a vicious circle. Narrowed retinal arteries and dilated retinal veins are known risk indicators for future cardiovascular events. As the major cause for retinal venous dilation is increased RVP, RVP may be an important marker.

Stodtmeister [29] recently documented a means to measure RVP with a contact lens dynamometer (Imedos, Jena, Germany). This device entails monitoring the retinal vein for pulsation while a pressure is applied to the sclera.

Until recently, the pressure in the intraocular veins was assumed to be equal to the IOP. According to Stodtmeister [30], the pressure in the central retinal vein may be considerably higher than the intraocular pressure. Therefore, the pressure in the retinal veins in the prelamellar layer of the optic nerve head is likely also higher than the IOP. In this case the perfusion pressure (arterial pressure minus central retinal venous pressure) is reduced (schematized in Figure 1). Since RVP is higher in glaucoma patients than in healthy subjects and in patients with unequal excavations, RVP is higher in the eyes with larger excavation, RVP is a considerable risk factor for the progression of glaucomatous damage. Such elevated RVP may be the reason IOP–lowering therapy is ineffective in eyes in which the pressure of the central retinal vein is higher than the intraocular pressure, a condition that may apply to about 40–50% of glaucoma patients [29,30].

Alternatively, angiography of the retinal vasculature at the optic nerve head could provide a viable assessment for
ocular blood flow. Optical coherence tomography angiography
(OCTA), a dye-free, non-invasive imaging assessment, has
recently been deployed to assess glaucomatous damage [31].
They showed that glaucomatous eyes had a reduced blood
flow and vessel density in the optic nerve head compared to
control eyes. Additionally, Wang, et al. [32] showed that OCTA
measurements correlate with visual field measurements,
indicating that OCTA provides a direct route to assessing retinal
perfusion. Thus, measurement of RVP and use of OCTA look to
be valuable tools in assessing retinal health in glaucoma.

Of course, retinal venous pressure can also be increased in a
clinically healthy eye. But nevertheless, it can be a strong sign
of a systemic disorder, such as an autoimmune disease [33].

The ocular cause of an increase of RVP may either be a
mechanical compression or a functional constriction of the
vein at the exit of the eye. The consequences are decreased
perfusion pressure, which increases the risk for hypoxia.
Increased RVP also increases transmural pressure and thereby
a risk for retinal edema.

Elevated RVP and elevated CSF pressure may have a
single cause or one may be influenced by the other. Morgan
[34] estimated the RVP effect by measuring the retinal vein
ophthalmodynamometric force, and found that it, and not
IOP, correlated with optic disc excavation. Morgan, et al. [35]
noted that high myopia patients have a thin lamina cribosa,
that this is exacerbated in myopic patients with glaucoma, and
that a thinner lamina cribosa magnifies the pressure gradient
effect by two to four times. This magnified effect may explain
the more rapid progression of glaucoma in myopic patients
including those having lower IOP.

In Fang, et al. [36], one frequent sign of NTG is an increase
of the retinal venous pressure (RVP). The effect of FS on RVP
was examined, measuring RVP in eyes of POAG patients and
healthy subjects with and without FS. Results showed that RVP
was higher in subjects with FS, particularly in FS subjects with
glaucoma.

Pillunat, et al. [37] evaluated patients with IOP-controlled
open angle glaucoma, examining those with early, moderate
and advanced disease stages and compared these to a healthy
control group. In more advanced cases of glaucoma, RVP was
higher than expected.

Sung [38] found progression in visual field loss in NTG
was related to an unstable ocular perfusion pressure (which
is proportional to RVP if IOP is static) by measuring IOP over a
24 hour period. They found that visual field defects in NTG are
more central than in patients with high IOP.

Treatment

Currently, the main goal of glaucoma treatment is the
slowing of disease progression with the goal of preserving
quality of life. The only tool to accomplish this has been
reduction of IOP, with several multicenter trials providing
evidence that reducing IOP slows the disease progression [1].

Thus, the recommended treatment for POAG, including
NTG, is to decrease IOP. Glaucoma treatment uses two
treatment strategies to reduce IOP: medication (topical or
systemic) and surgical shunts [39]. Additionally, minimally
invasive glaucoma surgery (MIGS) as well as cataract surgery
in NTG patients [40] have shown promise in slowing disease
progression. While IOP reduction is less effective for NTG,
it is the only treatment available to date, so the current best
practice is to lower IOP in NTG, with the American Academy
of Ophthalmology advising to lower IOP to 8–12 mmHg, and to
exercise caution in using beta blockers due to the comorbidity
of systemic nocturnal hypotension among NTG patients [41].

Decreasing IOP is minimally effective at preserving vision,
but given it is the only option, it is the current standard of care.
The evidence reported above that NTG presents with vascular
deficiencies gives hope that improving ocular perfusion may
be a potential treatment for NTG, as Fan, et al. [15] implies
and Chen, et al. [4] postulate. Similarly, the controlled study
showing an association between NTG and Flammer syndrome
[42] points to a vascular origin of NTG that may be related to
elication of endothelin-1 [16], who report measuring Flammer
syndrome in the eye by monitoring RVP.

A three month pilot study that directly tested this hypothesis
has proven effective in identifying NTG and presumed NTG
by the presence of elevated RVP [26]. Patients with elevated
homocysteine levels were included in the study. Treatment of
patients with Ocufolin® forte, (Aprofol, Switzerland) a vitamin
cocktail that reduces FS damage, was effective in lowering
homocysteine levels and reducing RVP. The reported values
in the course of their 3 month trial are reproduced in Figure 2, and
showed that RVP was reduced from 34.5 to 23.9 mm Hg, and
homocysteine levels were reduced from 16.4 to 12.7 μmol. The
Devogelaere, et al. [26] pilot study followed 23 patients (mean
age 70 y) for three months with daily Ocufolin forte. 16 patients
had confirmed glaucoma, and 3 were suspected glaucoma cases.
NTG cases were 7 of the 16 and 1 of the 3. RVP was calculated
from Ocular Dynamic Force (ODF) and IOP, using the formula
RVP = ODF + IOP.

While IOP dropped from 12.1 before the trial to 11.5 at the
conclusion of the trial, the decrease in RVP was striking. The
authors reported Ocufolin forte was well tolerated by the
patients and no side effects were observed. The findings of
Devogelaere, et al. [26] are included below this report.

Their results suggest that RVP screening of those at
risk for NTG is a viable evaluative method for this second
most common type of glaucoma. Further, they suggest that
addressing elevated RVP with Ocufolin is a valid approach for
NTG treatment.

Work by the Flammer team has previously shown that
in diabetic retinopathy there is an increase in retinal venous
pressure (RVP) which is related to retinal endothelial cell
damages [16]. A vitamin cocktail containing L-methylfolate
Ocufolin® forte, (Aprofol AG, Switzerland) lowered IOP and
Hcy in a three month trial with diabetic patients [24].

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Given the safety of this treatment, and the prevalence of currently untreatable NTG, we suggest consideration of the use of Ocufolin forte for diagnosed NTG cases with elevated RVP, in conjunction with regular monitoring of RVP and clinical evaluation of GON.

Conclusion

Given the link of RVP with NTG and other eye conditions, and the potential to treat RVP with a mixture of micronutrients having no known adverse effects, we suggest the use of RVP measurement or OCTA screening to assess for NTG in glaucomatous patients and to screen for early NTG in those with risk factors for local or systemic micronutrient deficiencies caused by various reasons. While RVP measurement may feel less comfortable for elderly patients than IOP measurements, it will permit the skilled ophthalmologist to identify and track NTG and to monitor treatment with the vitamin cocktail. We believe screening for FS characteristics will reduce RVP measurements to those at risk for NTG, and will allow the medical community to directly address this significant cause of blindness in a manner to reduce its impact. We suggest that glaucoma patients who are progressing despite adequate IOP control may benefit from RVP and homocysteine evaluation, in addition to the potential benefit of MIGS or early cataract surgery.

While the measurement of RVP is non–trivial, we believe it will be a useful tool for early diagnosis and for monitoring treatment of NTG, and provide a significant advance in treatment of this major cause of blindness.

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