American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Review Article

Ischemia from Retinal Vascular Hypertension in Normal Tension Glaucoma: Neuroprotective Role of Folate

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To Cite This Article: *George Ayoub* and Yanan Luo. Ischemia from Retinal Vascular Hypertension in Normal Tension Glaucoma: Neuroprotective Role of Folate. Am J Biomed Sci & Res. 2023 20(6) AJBSR.MS.ID.002786,* DOI: 10.34297/AJBSR.2023.20.002786

Received: November 24, 2023; **Published:** December 22, 2023

Abstract

Normal tension glaucoma is the most common form of glaucoma among people of Asian countries. While treatment to lower pressure in normal tension glaucoma is the standard of care, this is universally acknowledged as insufficient to the task. Recent evidence implicates ischemia and oxidative stress as key stressors of the optic nerve in normal tension glaucoma. Addressing ischemia and oxidative stress have been recommended as neuroprotective strategies. Elevated retinal venous pressure is found in normal tension glaucoma, and this venous hypertension is not adequately addressed with current medications. It increases resistance and reduces perfusion resulting in oxidative stress and localized ischemia. Elevated RVP appears to also be a factor in small vessel ischemia in diabetic retinopathy and macular degeneration.

The cause of elevated retinal venous pressure is small vessel endotheliopathy. Endotheliopathic damage may be caused by derangement of methylation and B-vitamin metabolism, resulting in altered microcirculation. This metabolic derangement may be due to either dietary inadequacies, malabsorption, or genetic polymorphisms of the methylation pathways. Restoration of folate and B-12 plasma levels may be accomplished with supplementation using natural forms of these vitamins, specifically L-methylfolate and methylcobalamin. Use of oxidized folate (folic acid) penetrates the blood retinal barrier only after enzymatic converstion of the folic acid to methylfolate. Since there is a limited capacity for folic acid conversion, excess folic acid remains unmetabolized and impedes methylfolate absorption into the retina. Thus, successful nutritional supplementation must employ methylfolate and not folic acid.

Such nutritional approaches are valuable adjuncts to standard ophthalmologic treatment, lowering retinal venous pressure and improving perfusion. Improved supply of micronutrients has implications for management of ischemic optic neuropathies, including normal tension glaucoma, nonarteritic ischemic optic neuropathy, and diabetic optic neuropathy and retinopathy.

Keywords: Normal tension glaucoma, Low tension glaucoma, Methyl folate, One-carbon metabolism, MTHFR polymorphism, Retinal venous pressure, Glaucoma, Blood-retina barrier, Retinal ischemia, Ocular ischemia, Diabetic retinopathy

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 and optic nerve blood flow is a feature of any glaucoma but in particular of NTG, a condition that results in Glaucomatous Optic Neuropathy (GON) and diminished visual field despite IOP in the normal range.

While IOP is normal in NTG, measurement of Retinal Venous Pressure (RVP) reveals elevated levels, which creates resistance, impairing retinal perfusion, and may contribute to glaucomatous optic neuropathy in NTG. Current treatment for NTG is limited to reduction in IOP, which is marginally effective, with many NTG pa-

tients eventually going blind. RVP increases are often associated with disturbed microcirculation. Evidence points to impaired autoregulation and alters endothelial cells, often seen also in subjects with Flammer Syndrome (FS). RVP measurement is a biomarker for NTG and may provide another screening tool.

Recent evidence with NTG patients has documented that the elevated RVP is reduced with a vitamin cocktail (Ocufolin forte, Aprofol AG) that includes the AREDS1 combination with certain B and D vitamins [1]. Ocufolin contains micronutrients, particularly L-methylfolate and methylcobalamin, and n-acetylcysteine (NAC, a glutathione precursor). It is well tolerated, with no reported moderate and/or serious adverse effects. We suggest RVP screening of those at risk for NTG and treatment of elevated RVP with Ocufolin as a viable adjunct treatment for NTG.

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 are likely greater than reported numbers [2]. 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 [3]. *Tham, et al.,* [4] projected an increase of 50% of all types of glaucoma in the next two decades. The CDC dataset on glaucoma provides important perspectives: https://www.cdc.gov/visionhealth/vehss/data/studies/glaucoma.html

The NHANES studies generate carefully validated population across sectional data and are among the most reliable sources for prevalence data. The NHANES 2005-2008 data set estimates that the prevalence of glaucoma in the US is 2.1% (2,900,000 individuals) [5]. The Beaver Dam study estimated the proportion of NTG to be 31.7% of all glaucoma [6]. Detailed data on global prevalence are provided by *Chen, et al.,* [7], *Tham, et al.,* [4] and *Kim, et al.,* [8]. Within Asian populations, 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 8. Diagnosis of NTG is determined from the presence of POAG signs such as damage to the optic nerve head in the presence of normal IOP.

In the *Wang, et al.,* [9] 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 [9]. 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. High tension glaucoma predominates in people with origins in Africa and Europe, while NTG predominates in people with origins in east Asia [6].

Clinical diagnostic markers for early glaucoma diagnosis are not universally agreed upon. Early glaucoma is often not detectable at a single screening visit, so it is underdiagnosed. These challenges make epidemiological data difficult to obtain and interpret. Medical clinics are full of patients with eye problems, increasing collection bias in many clinic-based studies.

Flammer Syndrome

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 (RVP) 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 [10]. Associated diseases are normal tension glaucoma, occlusion of ocular vessels, retinitis pigmentosa, multiple sclerosis, tinnitus or even sudden hearing loss.

Treatment of NTG

The standard treatment of NTG is too lower IOP with eye drops, control systemic risk factors and improve ocular perfusion. Severity of glaucoma is proportional to the severity of the cost burden. POAG showed higher median care and drug costs for severe POAG than mild POAG, and had higher risks for falls [11]. *Wang, et al.,* [9] provide guidance for treatment of NTG based on patient specifics.

Incremental Cost-Effectiveness Ratios (ICER) of treating NTG for disease progression have been determined. It is $34,225 (US) per Quality-Adjusted Life Year (QALY). The ICER for treating NTG patients with disc hemorrhage, migraine, and female sex were US $24,350, US $25,533, and US $27,000 per QALY, respectively [12]. It appears that IOP treatment of NTG is cost-effective for targeting a 30% reduction from the baseline [12].

Etiology

NTG, alternately termed low tension glaucoma or normal pressure glaucoma, manifests with ischemic optic disc flame hemorrhages and cupping, while IOP remains under 21 mmHg [13,14]. While NTG is generally considered to be similar to POAG in the outcomes, its etiology is different, and the initiating mechanism of damage is different from POAG with high IOP [6].

Evidence shows NTG damage to the retina appears to be due to a lack of perfusion, with reports of disrupted Ocular Blood Flow (OBF) [15] likely due to an increase in RVP causing damage to the axons of the retinal ganglion cells that comprise the optic nerve [2]. *Trivli, et al.,* [14] reviewed NTG pathogenesis, and developed a model 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). Wareham and Calkins [16] provided an excellent review detailing the impact of glaucoma on retinal vasculature, including diagrammatic clarity and the role of hormones on the endothelial cell making up the retinal arteries. Additionally, *Wang, et al.,* [17] explained that a pressure mismatch in POAG was created by either high IOP or low Cerebrospinal Fluid (CSF) pressure, resulting in a pressure gradient at the lamina cribosa that leads GON.

The work of *Fan, et al.,* [18,19] 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 [10,20]. *Fan, et al.,* [19] 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. Ocular Blood Flow (OBF) is on average less in glaucoma patients than in healthy controls. This reduction is more pronounced in normal-tension than in high-tension glaucoma, and it is more distinct in cases with progressing damage as compared to those with stable disease. OBF reduction has two effects on GON. The primary effect is a fluctuating supply of oxygen and micronutrients to the organs, leading to tissue damage. The fact that hypoxia-related factors are upregulated in eyes of glaucoma patients indicates oxygen depletion. It is, however, not constant hypoxia, but rather the fluctuation of the oxygen and micronutrient supply that leads to tissue damage, likely due to oxidative and nitrosative stress. Low perfusion pressure and disturbed autoregulation are major causes of the reduced blood supply causing oxygen and micronutrient variation, and both systemic hypotension and disturbed autoregulation are often consequences of the Primary Vascular Dysregulation Syndrome (PVD) [21,22]. The observed splinter hemorrhages in these patients are a consequence of a local breakdown of the Blood–Brain (BBB) or Blood–Retinal Barrier (BRB). The often associated vein occlusions can be a consequence of local vein dysregulation [23].

Gugleta, et al., [24] described the significance of endothelin-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 down-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 [16]. Flammer and Konieczka [20] evaluated the role of endothelin on RVP. In healthy subjects RVP is usually equal to or slightly above 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.

Retinal Venous Pressure and 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 GON [25].

In the Smith and Refsum comprehensive review of homocysteine as a disease biomarker (of various deficiencies), they find 100 diseases or conditions associated with raised concentrations of plasma homocysteine [26]. 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 becomes apparent if lowering plasma homocysteine by B vitamin treatment can reduce disease. Smith and Refsum [26] 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. Spence et al have reviewed several large homocysteine intervention studies, showing that ischemic stroke is preventable with homocysteine lowering from B-vitamin intervention, recommending the use of L-methylfolate and methylcobalamin. Homocysteine is more than a disease biomarker: it may be a useful guide for the prevention of disease [26,27].

The data in Schmidl [28] showed that a three-month intake of a dietary supplement containing L-methylfolate can sig¬nificantly 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.,* [29] gives the additional explanation of the utility of each component in the dietary supplement. Additionally, Lee et al demonstrate that NTG patients have a reduced retinal arterial pulse wave velocity [30]. Since pulsatile flow is more efficient in draining any cavity, this decreased pulse wave shows that the increased RVP shown by Devogeleare has a causative role in glaucomatous neuropathy by reducing retinal perfusion and drainage. With the demonstration that systemic L-methylfolate supplementation affects retinal perfusion in a pilot study [1], 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) [31] to NTG patients.

Homocysteine and endothelin-1 are also useful biomarkers for elevated RVP. As seen in Devogelaere, [1] homocysteine is elevated in NTG and other types of glaucoma. Efficient reduction of homocysteine with vitamin supplementation was already shown by Schmidl [28] in diabetic patients.

Measurement of RVP

Retinal Venous Pressure (RVP) may be measured non-invasively by ophthalmodynamometry [31,32] (few practices incorporate this measurement because it is difficult with available technology). While RVP is equal to or slightly above IOP in healthy people, it is often increased in patients with eye or systemic diseases, including glaucoma, retinal vein occlusion, diabetic retinopathy and primary vascular dysregulation. Beyond mechanical obstruction, the main

cause of such elevation is a local dysregulation of a retinal vein, believed to be venous vaso-constriction induced by endothelin-1 release. Generally, the main factors increasing endothelin-1 are inflammation and hypoxia.

Stodtmeister, et al., [33] 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, et al.,* [34], the pressure in the central retinal vein may be considerably higher than the IOP. Therefore, the pressure in the retinal veins in the prelaminar 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. 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 [35,36].

Alternatively, angiography of the retinal vasculature at the optic nerve head could provide a viable assessment for OBF. Optical Coherence Tomography Angiography (OCTA), a dye-free, non-invasive imaging assessment, has recently been deployed to assess glaucomatous damage [37]. 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.,* [38] 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. Another potential clinical evaluation for the decreased retinal perfusion seen in NTG may be direct observation of pulsation in the retinal vein [39]. Such observation has the advantage of being replicable in a trained clinician's office, and not entailing acquisition of a new technology to evaluate it.

Impact of Elevated Retinal Venous Pressure

Of course, RVP 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 [40]. 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, et al.,* [41] 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.,* [42] 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.,* [43], one frequent sign of NTG is an increase of the 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.,* [44] 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, et al.,* [44] 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.

Ischemia and Oxidative Stress

The Blood Retina Barrier (BRB) is composed of the retinal vascular endothelium and the Retinal Pigment Epithelium (RPE). Its integrity is closely linked to eye health. The persistent imbalance of oxidative stress in mitochondria causes functional and morphological impairments in RPE, endothelial cells, and Retinal Ganglion Cells (RGCs), and further breakdown BRB [45]. The supplementation of folate effectively restores the impaired endothelial-dependent vasodilation by lowering homocysteine level and attenuate oxidative stress, [46] thereby decrease ischemic injury and inflammatory injury of retina.

Folate, also known as vitamin B9, usually is provided from green leafy vegetables and animal liver. Folate deficiency increases the risk of dementia, cardiovascular disorders and optic neuropathy [47,48]. L-methylfolate is the primary bioactive form of folate and can be absorbed without any biological conversion in humans and can cross the BRB directly [49]. L-methylfolate is a donor of the methyl group involved in one-carbon metabolism, composed with folate cycle and methionine cycle (see Figure). It is critically important for DNA synthesis and methylation reactions [50]. The dysfunction of folate metabolism leads to the failure of converting homocysteine to methionine, the elevated homocysteine enhances intracellular oxidative stress. At the cellular level, elevated homocysteine disrupts the BRB and increases pigmented epithelial cell inflammatory cytokines, which cause retinal apoptosis [46,51]. Additionally, supplementation of L-methylfolate has also been reported to upregulate tetrahydrobiopterin (BH4) levels, which couple with Nitric Oxide Synthase Enzymes (eNOS) to generate nitric oxide. Nitric oxide is a cellular factor to regulate the vasodilation and increase the blood flow [52,53].

Folic acid is a synthetic form of folate and needs activation in the body. It goes through two steps of enzymatic process to generate L-Methylfolate: Dihydrofolate Reductase (DHFR) reduces folic acid to Tetrahydrofolate (THF) and then methyltetrahydrofolate

reductase (MTHFR) puts a methyl group to THF [54]. Bailey and Ayling's research have shown that DHFR in human body functions at a rather low efficiency [55]. Selhub and Rosenberg reviewed the evidence that a high intake of folic acid is linked to impaired cognition, memory, executive decision making, and retinoblastoma [56]. Moreover, MTHFR polymorphism is another obstacle to folic acid metabolism and results in unmetabolized folic acid (UMFA), which is reported to cause oxidative stress reversely [57]. MTHFR polymorphism is linked to an increase in the risk of retinal vascular disease. There are two predominant MTHFR polymorphisms, C677T and A1298C. According to previous reports, approximately 60-70% of the population have at least one of the variants [58]. Intake of L-methylfolate is unaffected by DHFR and MTHFR polymorphism and it is reported to be more efficient than folic acid for CNS homocysteine reduction, increasing nitric acid synthesis, and neuroprotection. Wang showed that supplement with the medical food Ocufolin, which contains L-methylfolate, significantly improved the retinal microcirculation of hypertensive retinopathy patients carring MTHFR polymorphisms [59,60] (Figure 1).

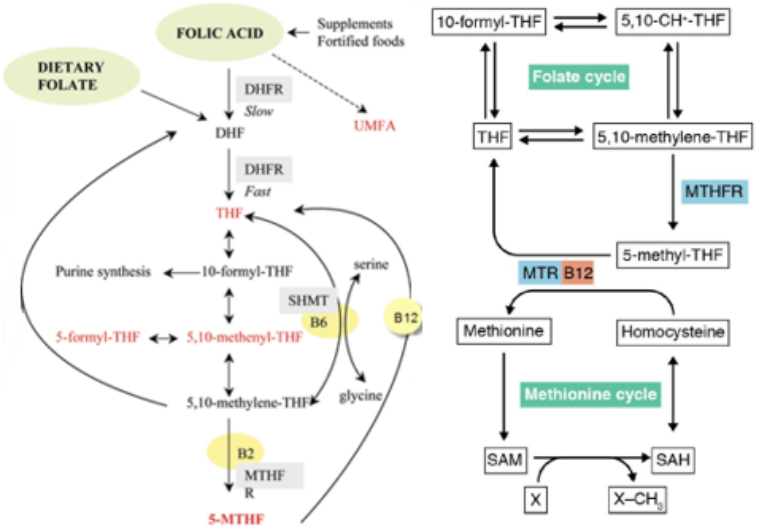

Figure 1: Metabolism of vitamin B 9 (Folate).

Lowering RVP is Augmentation of NTG Management

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 [2]. The recommended treatment for POAG, including NTG, is to decrease IOP, even if the level is in the normal range. Glaucoma treatment uses two strategies to reduce IOP: medication (topical or systemic) and surgical shunts [60]. Additionally, Minimally Invasive Glaucoma Surgery (MIGS) as well as cataract surgery in NTG patients [61] 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 [61].

Decreasing IOP is minimally effective at preserving vision, but it is the current standard of care. The evidence that NTG presents with vascular deficiencies gives hope that improving ocular perfusion may be a potential treatment for NTG, as *Fan, et al.,* [20] implies and *Chen, et al.,* [7] postulate. Similarly, the controlled study showing an association between NTG and Flammer syndrome [62] points to a vascular origin of NTG that may be related to elevation of endothelin-1 [1,21]. A three-month pilot study that directly tested this hypothesis proved effective in identifying NTG and presumed NTG by the presence of elevated RVP [1]. Patients with elevated homocysteine levels were included in the study. Additional treatment of patients with Ocufolin forte, (Aprofol, Switzerland) a vitamin cocktail, was effective in lowering homocysteine levels and reducing RVP. In the study, 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.,* [1] 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 more striking. The authors reported Ocufolin forte was well tolerated by the patients and no side effects were observed [1]. Their results suggest that RVP screening of those at risk for NTG is a viable evaluative method for this common type of glaucoma. Further, addressing elevated

RVP with Ocufolin is a valid approach for NTG treatment. Given the challenge of measuring RVP in an elderly patient, where immobility for 15 min is needed while the practitioner manipulates the orbit and constantly observes retinal vasculature, the promise of OCTA to view perfusion or of an AI system such as that under development by B. Zee (CUHK, personal communication) or some combination would be welcome. In the near term, we suggest observation by the skilled ophthalmologist to visually assess the presence of a retinal vein pulsation [38]. Given that perfusion is dependent on pulsatile flow, the ebbing of vascular pulsation would be cause for initiation of adjunct therapy with Ocufolin [63].

Work by the Flammer team has previously shown that diabetic retinopathy has an increase in RVP which is related to retinal endothelial cell damages [21]. A vitamin cocktail containing L-methylfolate (Ocufolin® forte, Aprofol AG) lowered IOP and homocysteine in a three-month trial with diabetic patients [29]. This suggests folate may have a neuroprotective function for glaucoma [64]. Given the safety of Ocufolin treatment, and the prevalence of currently untreatable NTG, we suggest consideration of the use of Ocufolin as an adjunct for diagnosed NTG cases with elevated RVP and/or decreased perfusion, in conjunction with regular monitoring of RVP and clinical evaluation of GON.

Conclusion

Given the link of RVP and homocysteine with NTG and other degenerative 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. Since RVP measurement may feel less comfortable for elderly patients than IOP measurement, using a proxy monitor of plasma homocysteine biomarker may be preferred until new technology under development become available. We believe screening for FS characteristics may provide guidance of 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.

The neuroprotective role of folate as an adjunct solution to maintain retinal perfusion may play a critical role in stabilizing the NTG patient and retaining vision. Folate, along with other vitamins, minerals and the antioxidants of the AREDS2 are beneficial in NTG. Folate reduces the elevated RVP, which thus restores retinal perfusion, reducing or eliminating the retinal ischemia present in NTG. We suggest application of a natural folate supplement, such as Ocufolin, be used as adjunct therapy in the standard treatment of NTG. The absence of any countereffects from this vitamin therapy indicates minimal patient risk.

Acknowledgement

None.

Conflict of Interests

None.

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