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Review Article

Managing Normal Tension Glaucoma with Dietary Folate

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Abstract

Normal-Tension Glaucoma (NTG) is the most prevalent form of glaucoma among individuals in Asian countries. While lowering intraocular pressure (IOP) remains the standard of care, this approach is insufficient for most NTG patients. Recent evidence documents the role of ischemia and oxidative stress as critical factors affecting the optic nerve in NTG. Consequently, addressing these factors has been recommended as a neuroprotective strategy.

While conventional treatment strategies primarily target the reduction of IOP, this yields limited efficacy and eventual blindness in many NTG cases. Recent studies document another crucial parameter: Retinal Venous Pressure (RVP). Elevated RVP impedes retinal perfusion, resulting in oxidative stress and localized ischemia, and exacerbating optic nerve damage in NTG. Elevated RVP also appears to be a contributing factor in small vessel ischemia associated with diabetic retinopathy and macular degeneration.

The underlying cause of elevated RVP is small vessel endotheliopathy, which may result from alterations in methylation and B-vitamin metabolism, leading to changed microcirculation. This metabolic disruption can arise from dietary inadequacies, malabsorption, or genetic polymorphisms affecting the methylation pathways. Restoring plasma levels of folate and B-12 can be achieved through supplementation with natural forms of these vitamins, specifically L-methylfolate, and methylcobalamin. Unlike oxidized folate (folic acid), which must be enzymatically converted to methylfolate to penetrate the blood-retinal barrier, L-methylfolate can be directly utilized. Excess unmetabolized folic acid can impede methyl folate absorption into the retina, underscoring the necessity of using methyl folate for effective supplementation.

We propose integrating RVP screening into NTG risk assessments and consider a targeted vitamin supplement, such as Ocufolin®, as a viable adjunct approach to manage elevated RVP and potentially mitigate NTG progression.

Introduction

Epidemiology

Glaucoma is a global health challenge, affecting more than 70 million individuals. It is the leading cause of irreversible blindness, with one in ten cases resulting in bilateral blindness. Often asymptomatic until advanced stages, the true prevalence of glaucoma may exceed reported figures [1]. Worldwide, all forms of glaucoma contribute 6.5% of blindness, with an overall prevalence of 3.5% among individuals aged 40 and older [2]. Tham, et al. [3]. project a 50% rise in glaucoma cases over the next two decades.

The NHANES studies provide robust population-based data on glaucoma prevalence, estimating it at 2.1% in the United States, equivalent to 2.9 million individuals [4]. The Beaver Dam Study indicates that normal tension glaucoma (NTG) constitutes approximately 31.7% of all glaucoma cases [5]. Detailed global prevalence data are extensively documented by Chen, et al. [6], Tham, et al. [3] and Kim, et al. [7].

In Asian populations, NTG represents a significant proportion of primary open-angle glaucoma (POAG), ranging from 70% in some East Asian countries to 50-70% in India and Nepal [7]. NTG diagnosis is characterized by signs of

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POAG, such as optic nerve damage, despite normal intraocular pressure (IOP).

Wang, et al. [8] provide a consensus assessment of NTG prevalence in China at 1%, comprising 70% of POAG cases in that country. They note lower average IOP values among Chinese populations compared to Caucasians, with NTG linked to characteristics resembling Flammer Syndrome (FS), including reduced intracranial pressure and impaired optic nerve perfusion at the lamina cribrosa.

Ethnic disparities are evident, with high-tension glaucoma more prevalent among individuals of African and European descent, contrasting with NTG's predominance in East Asian populations [5]. Challenges in early glaucoma detection underscore the need for consensus on clinical diagnostic markers, as the condition often eludes detection during initial screenings, contributing to underdiagnosis and complicating epidemiological data collection, particularly in clinic-based studies susceptible to selection bias.

Flammer syndrome

Flammer Syndrome (FS), frequently linked with Normal Tension Glaucoma (NTG), characterizes individuals with a predisposition to altered vascular responses triggered by stimuli such as cold, emotional stress, or high altitude. Common symptoms include cold extremities, low blood pressure, delayed onset of sleep, reduced thirst sensation, heightened sensitivity to odor, pain, vibration, and certain medications. Those affected by FS often exhibit traits of ambition, perfectionism, and occasional brooding.

Clinical features encompass altered gene expression, prolonged cessation of blood flow in nail fold capillaroscopy following cold exposure, impaired autoregulation of ocular blood flow, and reduced retinal vasodilation upon exposure to flickering light. Average Retinal Venous Pressure (RVP) tends to be elevated, with increased activation of retinal astrocytes observed in FS cases.

FS shows a predilection for females, thin individuals, younger age groups, graduates, and those with indoor occupations [9]. Associated conditions include NTG, ocular vessel occlusion, retinitis pigmentosa, multiple sclerosis, tinnitus, and occasionally sudden hearing loss. These insights underscore the multifaceted nature of FS and its clinical relevance in ophthalmology.

NTG treatment

The standard management approach for Normal Tension Glaucoma (NTG) involves reducing intraocular pressure (IOP) with topical medications, addressing systemic risk factors, and enhancing ocular perfusion. The economic impact of NTG correlates with disease severity; studies indicate higher median costs associated with severe primary open-angle glaucoma (POAG) compared to mild cases, along with increased risks of falls [10].

Wang et al. offer clinical insights tailored to individualized NTG treatment strategies. Incremental cost-effectiveness ratios (ICERs) have been calculated for NTG management aimed at preventing disease progression, with estimates showing $34,225 (US) per quality-adjusted life year (QALY). Specific ICERs for NTG patients presenting with disc hemorrhage, migraine, and female gender are reported at US $24,350, US $25,533, and US $27,000 per QALY, respectively [11]. These findings suggest that IOP-lowering therapy for NTG is cost-effective when targeting a 30% reduction from baseline levels [11].

Etiology

Normal tension glaucoma (NTG), also referred to as low tension glaucoma or normal pressure glaucoma, presents with characteristic ischemic optic disc changes such as flame hemorrhages and cupping, despite Intraocular Pressure (IOP) levels below 21 mmHg [11,12]. While NTG shares clinical outcomes similar to Primary Open-angle Glaucoma (POAG), its pathogenesis differs fundamentally, as the optic nerve damage in NTG is not primarily attributable to elevated IOP [13,14].

Research indicates that NTG-related retinal damage is associated with insufficient perfusion, often linked to disrupted Ocular Blood Flow (OBF) [15]. Elevated retinal venous pressure (RVP) is implicated in damaging the axons of retinal ganglion cells within the optic nerve [1].

Trivli, et al. [13] reviewed NTG pathogenesis, proposing a model where increased RVP reduces OBF, thereby impacting retinal ganglion cells and altering the optic nerve head. Wareham and Calkins [16] detailed the impact of glaucoma on retinal vasculature, emphasizing hormonal influences on endothelial cells in retinal arteries. Wang, et al. [17] highlighted how pressure mismatches, either high IOP or low cerebrospinal fluid (CSF) pressure, contribute to glaucomatous optic neuropathy (GON) via a pressure gradient at the lamina cribrosa.

Studies by Fan, et al. [18,19] underscore NTG's association with disturbed OBF as measured by imaging techniques and its comorbidity with systemic conditions like migraine, hypotension, Alzheimer's disease, and Flammer Syndrome [9,20]. They suggest that NTG may represent a spectrum of disorders with GON, posing implications for treatment approaches [19].

Ocular Blood Flow (OBF) reductions are more pronounced in NTG compared to high-tension glaucoma and correlate with disease progression rather than stability. This reduction results in fluctuating oxygen and nutrient supply to ocular tissues, potentially leading to oxidative and nitrosative stress. Disturbed autoregulation and systemic hypotension, often seen in Primary Vascular Dysregulation syndrome (PVD) [21,22] contribute significantly to compromised blood supply [23].

Endothelin-1, known for its vasoconstrictive effects, plays a crucial role in regulating blood vessel diameter in the retina and optic nerve, impacting blood flow [16,24]. Flammer and Konieczka [20] highlighted the role of endothelin-1 in influencing RVP, noting its potential as a biomarker alongside homocysteine in evaluating vascular dynamics.

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In summary, understanding the complex interplay of vascular factors and biomarkers like endothelin-1 and homocysteine offers insights into NTG pathophysiology and guides therapeutic strategies aimed at preserving ocular perfusion and mitigating optic nerve damage.

Homocysteine and RVP

Elevated homocysteine levels and the prevalence of heterozygous methylene-Tetrahydrofolate Reductase (MTHFR) C677T mutation are associated with Open-angle Glaucoma (OAG). Homocysteine, which is linked to vascular injury, alteration of extracellular matrix remodeling, and promotion of neuronal cell death, holds implications for understanding Glaucomatous Optic Neuropathy (GON) [25].

Smith and Refsum extensively reviewed homocysteine as a biomarker across various diseases, identifying over 100 conditions linked to elevated plasma homocysteine levels [26]. These associations predominantly involve cardiovascular and central nervous system disorders, as well as developmental and age-related conditions. The clinical significance of homocysteine is underscored by evidence that reducing its levels through B vitamin therapy can mitigate several diseases, including neural tube defects, impaired childhood cognition, macular degeneration, stroke, and cognitive decline in the elderly. They suggest that maintaining plasma homocysteine levels below 10 µmol/L is likely safe, while levels at or above 11 µmol/L may warrant intervention.

Intervention studies reviewed by Spence et al. demonstrate the preventability of ischemic stroke through homocysteine reduction via B-vitamin supplementation, specifically L-methylfolate, and methylcobalamin. This approach supports the potential role of homocysteine as more than a biomarker but as a guide for disease prevention [26,27].

Schmidl, et al. [28] showed that L-methylfolate supplementation significantly reduces blood homocysteine levels in diabetic patients over three months, highlighting its relevance in mitigating vascular-related systemic and ocular diseases. Nutritional therapies, as reviewed by Shi, et al. [29], further underscore the therapeutic potential of dietary supplements in managing conditions like diabetic retinopathy.

Lee, et al. [30], demonstrated that patients with Normal Tension Glaucoma (NTG) exhibit reduced retinal arterial pulse wave velocity, indicating compromised retinal perfusion. This reduction in pulsatile flow suggests a contributory role of elevated Retinal Venous Pressure (RVP), as highlighted by Devogelaere [31], in glaucomatous neuropathy by impairing retinal perfusion and drainage.

Given these insights, homocysteine and endothelin-1 emerge as valuable biomarkers for assessing elevated RVP in NTG and other glaucoma types. Effective reduction of homocysteine through vitamin supplementation, as demonstrated by Schmidl [28], supports its potential role in managing glaucoma and related vascular disorders.

RVP measurement

Retinal Venous Pressure (RVP) can be assessed non-invasively using ophthalmodynamometry [32,33], although its adoption remains limited due to technological challenges. While RVP typically mirrors or slightly exceeds intraocular pressure (IOP) in healthy individuals, it often rises in patients with ocular or systemic conditions such as glaucoma, retinal vein occlusion, diabetic retinopathy, and primary vascular dysregulation. This elevation is primarily attributed to localized dysregulation of retinal veins, likely induced by endothelin-1-mediated venous vasoconstriction, exacerbated by factors like inflammation and hypoxia.

Stodtmeister [34] recently introduced a contact lens dynamometer (Imedos, Jena, Germany) for measuring RVP and monitoring retinal vein pulsations under scleral pressure. Contrary to prior assumptions, their work indicates that pressures in the central retinal vein can significantly surpass IOP levels, particularly within the prelaminar optic nerve head region. Elevated RVP is associated with larger optic nerve excavations and is a significant risk factor for progressive glaucomatous damage, potentially explaining cases where IOP-lowering therapies prove ineffective-estimated to affect 40% - 50% of glaucoma patients [34,35].

Alternatively, Optical Coherence Tomography Angiography (OCTA), a non-invasive imaging technique, offers a promising approach to assess retinal perfusion at the optic nerve head without dye injection [36]. Studies employing OCTA have demonstrated reduced blood flow and vessel density in glaucomatous eyes compared to controls. OCTA measurements have also shown correlations with visual field assessments, highlighting its utility in evaluating retinal health [37].

Further, direct observation of retinal vein pulsation provides another feasible clinical method for assessing decreased retinal perfusion in conditions like Normal Tension Glaucoma (NTG). This technique offers the advantage of reproducibility in a clinician's office setting without requiring specialized equipment.

In sum, integrating RVP measurement, OCTA, and direct observation of retinal vein pulsation into clinical practice holds promise for advancing the assessment of retinal health and guiding treatment strategies in glaucoma and related conditions [38].

Effect of elevated RVP

Certainly, elevated Retinal Venous Pressure (RVP) can manifest even in clinically healthy eyes, yet it may signal an underlying systemic disorder, such as autoimmune disease [39].

The ocular causes of increased RVP can include mechanical compression or functional constriction of the retinal vein at its exit from the eye. These conditions lead to decreased perfusion pressure, heightening the risk of ocular hypoxia. Elevated RVP also raises transmural pressure, increasing the likelihood of retinal edema.

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The relationship between elevated RVP and Cerebrospinal Fluid (CSF) pressure is noteworthy, as they may share a common influence or one may impact the other. Morgan demonstrated the impact of RVP on optic disc excavation using ophthalmodynamometric measurements of retinal vein force, highlighting its correlation with glaucomatous optic neuropathy independent of Intraocular Pressure (IOP) [40]. Further, Morgan et al. noted that patients with high myopia exhibit a thin lamina cribrosa, exacerbating the pressure gradient effect and potentially accelerating glaucoma progression even with lower IOP [41].

In the context of Normal Tension Glaucoma (NTG), Fang, et al. [42], observed that elevated RVP is a frequent characteristic, particularly in individuals with Flammer Syndrome (FS), a condition associated with heightened RVP, especially in those with glaucoma.

Pillunat, et al. [43], evaluated open-angle glaucoma patients with controlled IOP across different disease stages, revealing higher-than-expected RVP levels in advanced glaucoma cases compared to healthy controls.

Sung's [44] findings linked visual field deterioration in NTG to unstable ocular perfusion pressure, which correlates with RVP when IOP remains stable. Their study suggested that NTG patients experience more centrally located visual field defects compared to individuals with high IOP.

In sum, monitoring RVP provides valuable insights into ocular and systemic health, informing clinical management strategies, especially in conditions like glaucoma where perfusion dynamics play a critical role in disease progression.

Discussion

The blood-retina barrier (BRB) consists of the retinal vascular endothelium and the Retinal Pigment Epithelium (RPE). Its integrity is essential for overall eye health. Persistent oxidative stress in mitochondria can lead to functional and morphological impairments in the RPE, endothelial cells, and Retinal Ganglion Cells (RGCs), compromising the BRB [45]. The oxidative stress can be mitigated by lowering homocysteine levels via folate supplementation [46].

Role of folate in retinal health

Folate, or vitamin B9, is typically obtained from green leafy vegetables and animal liver, among other sources. A folate deficiency can increase the risk of dementia, cardiovascular disorders, and optic neuropathy [47,48]. The primary bioactive form of folate, L-methylfolate, is directly absorbable and can cross the BRB without requiring biological conversion [49].

L-methylfolate is crucial for one-carbon metabolism, which includes the folate cycle and methionine cycle, and plays a vital role in DNA synthesis and methylation reactions [50]. When folate metabolism is disrupted, homocysteine cannot be efficiently converted to methionine, leading to elevated homocysteine levels and increased intracellular oxidative stress. Elevated homocysteine disrupts the BRB, increases inflammatory cytokines in pigmented epithelial cells, and induces retinal apoptosis [46,51].

Mechanisms of L-methyl folate supplementation

L-methylfolate supplementation has been shown to lower homocysteine levels and attenuate oxidative stress, thereby restoring impaired endothelial-dependent vasodilation. This reduces ischemic and inflammatory injuries to the retina. Additionally, L-methylfolate upregulates tetrahydrobiopterin (BH4) levels, which enhance nitric oxide synthesis through coupling with endothelial Nitric Oxide Synthase (eNOS). Nitric oxide is vital for vasodilation and improved blood flow [52,53].

Folic acid *versus* L-methyl folate

Folic acid, the synthetic form of folate, must undergo two enzymatic conversions to become L-methylfolate. These steps involve Dihydrofolate Reductase (DHFR) and Methyltetrahydrofolate Reductase (MTHFR) [54]. However, DHFR operates inefficiently in humans [55] and high folic acid intake is associated with impaired cognition and an increased risk of retinoblastoma [56]. Furthermore, MTHFR polymorphisms, present in 60-70% of the population, hinder folic acid metabolism and lead to Unmetabolized Folic Acid (UMFA), which can paradoxically cause oxidative stress [57]. MTHFR polymorphism is tied to an elevated risk of retinal vascular disease. The two most common MTHFR polymorphisms, C677T and A1298C, are present in 60-70% of the population [58].

In contrast, L-methylfolate supplementation bypasses the enzymatic conversions, making it readily available for reducing homocysteine levels, enhancing nitric oxide synthesis, and providing neuroprotection. Research has shown that supplementation with medical foods like Ocufolin®, which contains L-methylfolate, significantly improves retinal microcirculation in hypertensive retinopathy patients with MTHFR polymorphisms [59].

NTG management by decreasing RVP

The primary objective in glaucoma treatment today is to slow disease progression and preserve the quality of life. The principal strategy for achieving this has been the reduction of Intraocular Pressure (IOP), supported by evidence from multiple multicenter trials indicating that lowering IOP can decelerate the disease's progression [2].

The recommended treatment for Primary Open-angle Glaucoma (POAG), including normal-tension glaucoma (NTG), involves decreasing IOP, even when it is within the normal range. Two main strategies are employed to reduce IOP: medication (topical or systemic) and surgical interventions such as shunts [60]. Additionally, Minimally Invasive Glaucoma Surgery (MIGS) and cataract surgery in NTG patients have shown promise in slowing disease progression [61]. Although IOP reduction is less effective for NTG, it remains the only available treatment. The American Academy of Ophthalmology advises lowering IOP to 8-12 mmHg for NTG patients while exercising caution with beta-blockers due to the comorbidity of systemic nocturnal hypotension [62].

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While decreasing IOP is currently the standard of care, its efficacy in preserving vision for NTG patients is limited. The vascular deficiencies observed in NTG offer hope that improving ocular perfusion might serve as a more potent treatment. Studies by Fan, et al. [20] and Chen, et al. [7] suggest this possibility, while a controlled study linking NTG and Flammer syndrome [63] highlights a vascular origin potentially related to elevated endothelin-1 levels [21,31].

Clinical control of RVP and homocysteine

A three-month pilot study aimed to test this hypothesis by identifying NTG and presumed NTG based on elevated Retinal Venous Pressure (RVP) [31]. Patients with elevated homocysteine levels were included in the study. Treatment with Ocufolin® forte (Aprofol, Switzerland), a vitamin cocktail, effectively lowered both homocysteine levels and RVP. In this study, RVP decreased from 34.5 to 23.9 mmHg, and homocysteine levels dropped from 16.4 to 12.7 µmol. The pilot study by Devogelaere, et al. [31], involved 23 patients (mean age 70 years), of whom 16 had confirmed glaucoma, including 7 NTG cases. RVP was calculated using ocular dynamic force (ODF) and IOP, with the formula RVP = ODF + IOP.

Although IOP decreased slightly from 12.1 to 11.5 mmHg, the reduction in RVP was more substantial. The study reported that Ocufolin® forte was well tolerated, with no observed side effects [31]. These results suggest that RVP screening for NTG risk is a useful evaluation method, and addressing elevated RVP with Ocufolin® is a viable treatment approach.

Best practice for RVP control

Given the challenges of measuring RVP in elderly patients, alternative methods such as OCTA to assess perfusion or AI systems currently under development could be beneficial. In the near term, skilled ophthalmologists may visually assess retinal vein pulsation [38], to guide the initiation of adjunct therapy with Ocufolin when necessary [64].

Previous work by the Flammer team has shown that diabetic retinopathy involves increased RVP linked to retinal endothelial cell damage [20]. A vitamin cocktail containing L-methylfolate (Ocufolin® forte, Aprofol AG) has been effective in lowering IOP and homocysteine in diabetic patients [28], suggesting a potential neuroprotective role for folate in glaucoma management [65].

Given the safety profile of Ocufolin® treatment and the prevalence of currently untreatable NTG, we recommend considering Ocufolin® as an adjunct therapy for diagnosed NTG cases with elevated RVP and/or decreased perfusion, alongside regular RVP monitoring and clinical evaluation of Glaucomatous Optic Neuropathy (GON).

Conclusion

Given the association of Retinal Venous Pressure (RVP) and homocysteine with Normal-tension Glaucoma (NTG) and other degenerative eye conditions, and the potential to manage RVP with a mixture of micronutrients that have no known adverse effects, we propose the use of RVP measurement or Optical Coherence Tomography Angiography (OCTA) screening to assess for NTG in glaucomatous patients. Further, this approach can be used to screen for early NTG in individuals with risk factors for local or systemic micronutrient deficiencies.

Since RVP measurement may be less comfortable for elderly patients compared to Intraocular Pressure (IOP) measurement, using a plasma homocysteine biomarker as a proxy monitor may be preferred until newer, more comfortable technologies become available. Screening for FS (Flammer Syndrome) characteristics may provide valuable guidance in identifying those at risk for NTG and allow the medical community to address this significant cause of blindness more effectively.

The neuroprotective role of folate as an adjunct therapy to maintain retinal perfusion may be crucial in stabilizing NTG patients and preserving vision. Folate, along with other vitamins, minerals, and antioxidants from the AREDS2 (Age-Related Eye Disease Study 2) formula, has shown benefits in NTG management. Folate reduces elevated RVP, thereby restoring retinal perfusion and reducing or eliminating the retinal ischemia present in NTG. We recommend the use of a natural folate supplement, such as Ocufolin®, as an adjunct therapy in the standard treatment of NTG. The absence of adverse effects from this vitamin therapy indicates minimal risk to patients.

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