

American Academy of Optometry: Case Report 3

Normal Tension Glaucoma

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Abstract

Normal tension glaucoma (NTG) can be defined as a characteristic glaucomatous optic neuropathy occurring in the presence of normal intraocular pressure (IOP). The development and subsequent diagnosis of glaucoma with IOP levels historically considered normal (≤ 20 mm Hg) suggests and only enhances a theory of disease progression primarily being the result of optic nerve pathology. Examples of possible contributing factors include systemic non-inflammatory and inflammatory vascular disease, carotid disease, cardiac disease, hematologic disorders, pulmonary disease, metabolic conditions, demyelinating disease, orbital disease, trauma, surgery, age, and genetic variants. Particularly with NTG, understanding the disease process from an oculosystemic perspective is fundamental in determining appropriate treatment strategies allowing for neuro-protection of the optic nerve. Therefore, in addition to IOP reduction, the prevention of progressive glaucomatous optic neuropathy in NTG may ultimately require a multi-disciplinary team approach to provide adequate therapy and preservation of vision.

Keywords: *Glaucoma, Glaucomatous Optic Atrophy, Glaucomatous Optic Neuropathy, Intraocular Pressure, IOP, Ischemic Optic Neuropathy, ION, Normal Tension Glaucoma, NTG, Oculosystemic Disease*

Introduction

Normal tension glaucoma (NTG) can be described as a glaucomatous optic neuropathy occurring with a baseline intraocular pressure (IOP) of ≤ 20 mm Hg present at the time of initial diagnosis. However, it can be argued that NTG is not a separate entity but can be considered a primary glaucoma based on current definitions which exclude IOP. Therefore, the term “normal tension glaucoma” can be considered a misnomer which only characterizes a variation of glaucoma in its truest form. That which produces optic nerve pathology, retinal nerve fiber layer (RNFL) deficits, and subsequent loss of visual field.

Regarding ocular hypertension (OHT) associated with the primary glaucoma's, pre-treatment IOP of ≥ 21 mm Hg has historically been thought of as the leading risk factor in the development of progressive glaucomatous optic neuropathy. OHT is indeed one of many contributing risk factors; however, its importance has been scrutinized in recent years and has also led to a re-thinking and re-defining of the glaucomatous condition.

Considering the significant incidence and prevalence of the glaucomas occurring within a wide range of baseline IOP's, a paradigm shift in language defining glaucoma omitting the term “intraocular pressure” has been universally accepted. Known multi-factorial contributors to etiology and disease progression further de-emphasize the role of initial IOP levels. Furthermore, glaucomatous visual field defects may or may not be present depending on the severity of associated optic neuropathy.

The American Optometric Association (AOA) explains glaucoma as a chronic progressive disease that most often presents with characteristics of optic nerve, RNFL and visual field loss. Similarly, the American Academy of Ophthalmology (AAO) describes glaucoma as a multi-factorial optic nerve neuropathy in which there is a characteristic acquired loss of optic nerve fibers. It is of interest to note that visual field loss is not a required finding according to the AAO definition, but of course visual field loss is the eventual result of progressive disease.

It is important to understand the dynamics of associated ocular and systemic conditions that must be maintained in order to provide a balanced relationship at the level of the optic nerve head (ONH). It is this synergistic environment which promotes and allows for continued integrity, function and vision. In contrast, vascular, hematologic, metabolic, axonal, or mechanical insults affecting the ONH can disrupt this balance; potentially allowing for progressive glaucomatous optic neuropathy to occur. A genetic predisposition may also be present leading to increased susceptibility for characteristic neuropathy. Increasing age is an additional factor that should be considered.

Commonly, ischemic conditions produced by non-arteritic or arteritic vascular disease are discovered as an underlying feature in the NTG clinical presentation. Carotid obstruction or giant cell arteritis (GCA) with associated temporal arteritis can often be associated with unilateral or asymmetric cases. In fact, there may not be a clear distinction between ischemic optic neuropathy (ION) and NTG under certain clinical conditions.

It is important that untreated or refractory systemic disease propagating NTG be promptly identified and addressed. Due to the high association with vascular disease, proper diagnostic and radiologic testing as well as communications with appropriate specialists is a priority. Normal tension glaucoma managed correctly can not only lead to vision saving outcomes, but in certain circumstances can lead to life saving treatments.

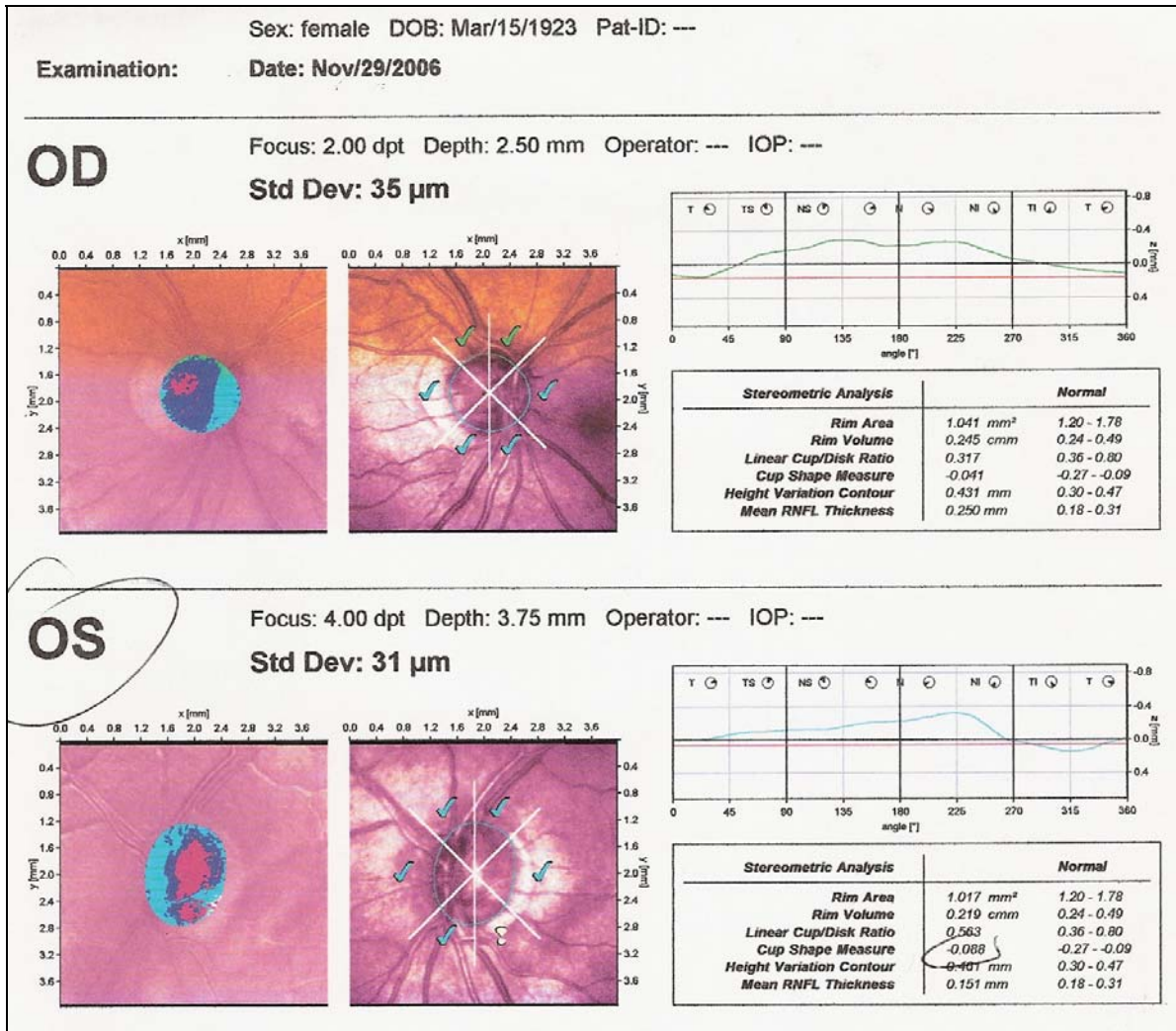
Case Report

An 83 year old caucasian lady presented for a routine examination on November 29, 2006. Her chief complaint was "I sometimes have a film over my left eye". She was uncertain of when her vision had changed. She previously underwent uneventful cataract surgery with posterior chamber intraocular lens (PC IOL) placement in both eyes in 2003; otherwise, she had no significant ocular history. She was being treated for hypertension and hypercholesterolemia which was controlled with Accupril (Quinapril) 20mg PO QD and Lipitor (Atorvastatin) 20mg PO QD. She reported having a mother who was diagnosed with glaucoma and cataracts. She did not reveal an additional ocular or systemic family history.

Best corrected visual acuity with refraction was 20/20 OD and 20/25 OS NIPH. Color plates were normal for each eye. Stereopsis was normal. Confrontation visual fields were full OD, however, there was evidence of a mild infero-nasal constriction OS. Pupils were equal, round, and responsive to light and accommodation. There was no afferent pupillary defect elicited OS. Extraocular muscle versions were full and unrestricted without subjective diplopia. Biomicroscopic examination revealed a healthy anterior segment with a well placed posterior chamber phacoprosthesis in each eye. There was a slightly reduced tear break-up-time (BUT) of 9 seconds OU indicating a mild evaporative dry eye. Goldmann applanation tonometry was 16mm Hg OD and 18mm Hg OS. Goldmann 3-mirror gonioscopy showed a grade IV open angle in all four quadrants OU. All angle structures were viewed in each eye including Schwalbe's line, trabeculum, Schlemm's canal, scleral spur, and ciliary body. There was trace pigment present within the trabeculum OU without evidence of pseudoexfoliative debris in either eye. The anterior chamber was found to be clear and quiet without sign of current or previous ocular inflammatory activity OU. Dilated 90D ophthalmoscopic evaluation showed a clear vitreous in each eye, however, a posterior vitreous detachment (PVD) and Weiss ring was apparent OU. The periphery was normal in each eye. Early involutinal and hypertensive arteriolar sclerotic retinal vascular changes with arterio-venous nicking could be appreciated OU. The macula in each eye showed early dry age related degenerative changes (ARMD) with retinal pigment epithelial (RPE) hyperplasia and peri-foveal drusen. The optic disc OD was found to be asymmetric with respect to smaller disc diameter and less cupping compared to the fellow eye. A c/d of 0.3/0.3 was viewed in the right eye. The optic disc OS was found to have advanced vertical cupping extending inferiorly with significant thinning of neuro-retinal rim tissue in the lower quadrant. A c/d of 0.5/0.8 was viewed in the left eye. Early optic disc pallor was also present OU.

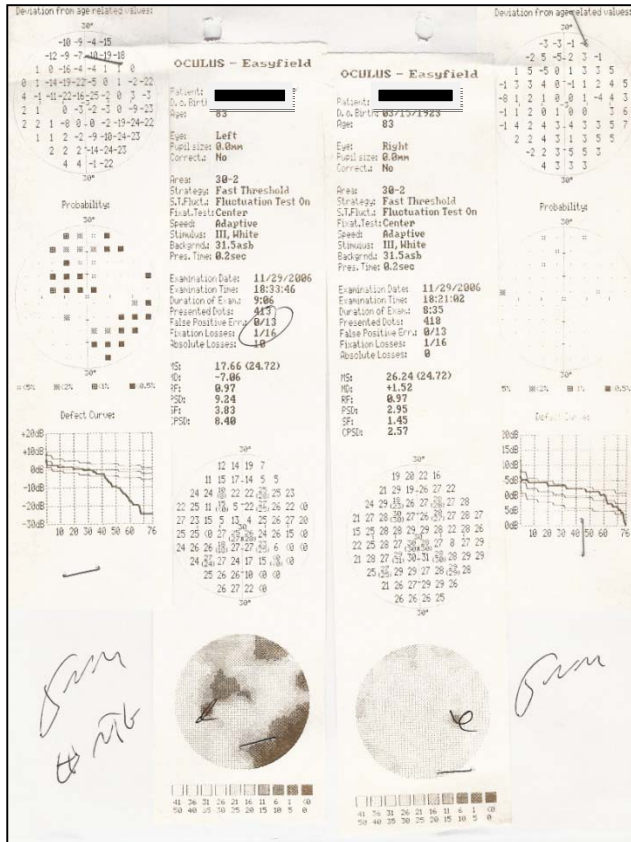
Based on the above findings, a preliminary diagnosis of NTG OU > OS was suspected. Pachymetry measurements were then obtained being quite favorable at 664 μ OD and 654 μ OS. ONH Heidelberg retinal tomography (HRT) analyses was also performed confirming asymmetric advanced glaucomatous optic cupping present in the left eye with significantly reduced mean RNFL thickness; particularly in the infero-temporal and temporal quadrants. Interestingly, the

right ONH demonstrated better unique stereometric analyses; however, the global cup shape measure (CSM) was actually further from normal compared to the left suggesting impending progression.



Digital stereoscopic photographs also showed asymmetric glaucomatous optic neuropathy OU > OS with slight optic pallor present OU. 30-2 threshold visual fields were performed which was full OD but revealed an early characteristic glaucomatous Bjerrum scotoma along with a nasal step defect OS. The visual field loss correlated nicely with the ONH HRT and photographic evidence in the left eye.

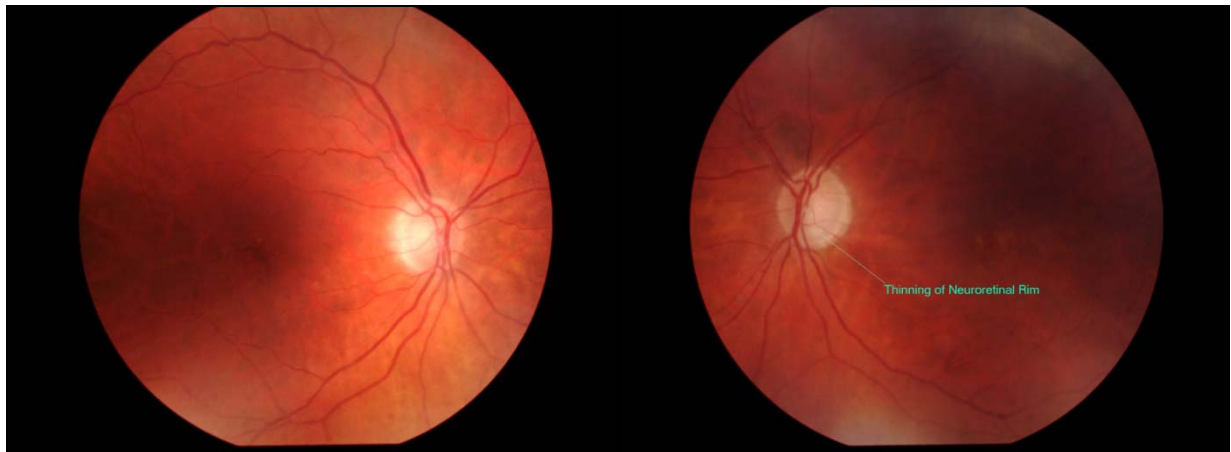
While taking into account the slight acuity reduction in the left eye, a definitive diagnosis of normal tension glaucoma OU, advanced OS, with early secondary glaucomatous optic atrophy vs. ION OS was concluded. The reduction in acuity in the left eye could also be attributed to the early dry ARMD observed. Due to the marked asymmetry OS with mild micro-vasculopathy and optic pallor present in each eye, an underlying systemic contributor must be ruled-out. Considering her history of hypertension and elevated cholesterol, an ischemic vascular component was first pursued and a treatment plan consisting of the following was recommended.



1. Travatan (Travoprost 0.004%) 1 gtt HS OU
2. Carotid Doppler, emphasis (L)
3. MRI Head/Orbits, emphasis (L) Orbit
4. Bloodwork:
 - *CBC w/diff
 - *SMA-20
 - *ESR
 - *Protein C (CRP) + S
 - *ANA
 - *PT/PTT
5. Amsler Grid
6. Ocuvites as directed
7. Artificial Tears 1 gtt PRN OU

She was advised of the likelihood for additional topical adjunctive therapy as well

as selective laser trabeculoplasty (SLT) treatment in order to achieve a proper target pressure. A goal of ≤ 12 mm Hg OU was set equating to a 25% and 33% reduction respectfully; being an effectual drop for the left eye. In addition to the laboratory studies, an MRI of the head and orbits was also be required to rule-out associated ischemic cerebro-vascular disease and/or compressive orbital disease OS. Although she reported no history of demyelinating disease, the possibility of previous recurrent optic neuritis OS is also a consideration allowing for greater probability of glaucomatous progression in that eye. The MRI results would provide further insight in this regard as well. She was encouraged to follow-up with her primary care physician (PCP) with a report of these findings and to re-evaluate her blood pressure, cholesterol levels, cardiovascular, and general health.



She was scheduled for a 1 month return visit to reassess VA, IOP, and to review laboratory findings.

Follow-up #1

She returned as scheduled for her 1 month follow-up visit. She had recently seen her PCP who reported her general health as being stable with adequate blood pressure and cholesterol control and without contributing cardiovascular disease. She stated no changes in her vision and acknowledged being compliant with her topical treatment. Doppler findings were non-contributory demonstrating 16% - 39% of external and internal carotid stenosis on each side without evidence of asymmetry. Her bloodwork returned unremarkable without suggestion of disseminating inflammatory disease, disorders of coagulation, or blood dyscrasia. Corrected VA remained 20/20 OD and 20/25 OS. Interestingly, her Goldmann applanation IOP increased in the right eye to 19mm Hg and was unchanged at 18mm Hg in the left.

Despite the laboratory findings and the PCP's report; her age, hypertension, hypercholesterolemia, retinal micro-vasculopathy, and presence of optic pallor is suggestive of ischemic conditions. Therefore, in this case, Travatan was continued due to the possibility of improved ocular bloodflow rather than IOP efficacy.¹ Additionally, Azopt (Brinzolamide 1%) 1 gtt Q12H OU was added as was the recommendation of SLT treatment OU to help attain our target IOP. She was scheduled to return in 1 month to re-evaluate her VA, IOP, and to perform SLT OS.

Follow-up #2

She returned as scheduled for her 1 month visit. She reported no change in her vision and confirmed her compliance with both topical medications. Corrected VA was stable at 20/20 OD and 20/25 OS. IOP OD was unchanged from initial baseline at 16mm Hg but reduced to 15mm Hg OS signifying some response to the dual topical treatment. A 40mw/400μ 100 spot SLT treatment was applied 360° to the OS trabeculum. As is our protocol to facilitate responsiveness, no additional post-operative topical medications were recommended. She was instructed to continue Travatan and Azopt as prescribed and was scheduled for a 10 day post-operative visit to include SLT OD.

Follow-up #3

She returned as scheduled for her 10 day post-operative visit. She continued to be compliant with her topical treatment and was asymptomatic following SLT OS. Her corrected vision remained 20/20 OD and 20/25 OS. Her IOP on this visit was further decreased to 13mm Hg OD and 12mm Hg OS representing a 19% and 33% drop respectfully from baseline. With target pressure achieved OS, the OD received the same 40mw/400μ 100 spot SLT treatment applied 360° to the trabeculum. As before, no additional post-operative topical medications were recommended and she was asked to return in 10 days.

Follow-up #4

She returned as scheduled for her 10 day post-operative visit. She was compliant with her topical medications and was asymptomatic following SLT OD. Corrected VA was the same at 20/20 OD and 20/25 OS. IOP was now found to be 11mm Hg OD and 12mm Hg OS. The OD reduction now represented a 31% drop from baseline with target pressure successfully achieved in both eyes.

In addition to sustaining her topical therapy, she was educated of the importance for scheduled IOP, HRT, photography, and visual field testing. She was reminded of her early dry ARMD and the relevance to her central acuity. A baseline macular HRT analyses was scheduled for a later date and she was re-instructed on using the Amsler grid at home as well as continuing the vitamin therapy. Finally, an MRI of the head and orbits was once again recommended with an order written to rule-out associated ischemic cerebro-vascular and/or orbital disease. She had been hesitant to pursue this avenue although the significance was emphasized with respect to providing a more complete assessment of her condition.

Discussion

Normal tension glaucoma can be considered part of a continuum of the primary glaucomas with respect to current defining criteria omitting the term “intraocular pressure”.² The presence of glaucomatous optic nerve damage, retinal nerve fiber layer deficits, with or without characteristic visual field defects is now known to be possible at any intraocular pressure. Therefore, an intrinsic predisposition with respect to structure, integrity, and susceptibility of the ONH and RNFL must first be present for eventual pathology to develop. An asymmetric presentation may be indicative of more advanced systemic, orbital, or ocular disease occurring on the same side as the further progressed neuropathy. True for all glaucomas, the presence of glaucomatous optic neuropathy must not be assumed isolated and independent of other conditions. A wholistic oculosystemic approach should be maintained with causative factors considered in the therapeutic methodology.

The clinical presentation of NTG may be easily overlooked if the practitioner is relying on intraocular pressure as the sole initial diagnostic indicator for glaucoma. In line with current thinking, the clinical relevance of baseline IOP in all patients should be viewed as only one of many diagnostic features when assessing the optic nerve. By definition, it is the study and scrutiny of the optic nerve itself and RNFL integrity which are first and foremost in making proper diagnostic decisions. Importantly, generalized oculosystemic considerations such non-inflammatory and inflammatory vascular disease, carotid disease, cardiac disease, hematologic disorders, pulmonary disease, metabolic conditions, demyelinating disease, orbital disease, ocular disease, trauma, surgery, age, and genetic variants can all play a part in the proper diagnosis, management, and prognosis. Therefore, the treatment of these same conditions may be equally vital for neuro-protection of the optic nerve as is ocular hypotensive measures. A thorough understanding of appropriate laboratory and radiologic testing is mandatory along with proper communications with relevant specialists in order to achieve an individualized management plan.

Asymmetric or unilateral cases of NTG should be viewed with additional prudence regarding etiology. The possibilities of ipsilateral orbital compressive disease, carotid stenosis, underlying arteritic or non-arteritic ischemic optic neuropathy with simultaneous optic pallor and cupping are only some of the more common clinical scenarios. Relevant targeted laboratory and radiologic testing is particularly helpful in these cases which may lead to uncovering a previously unknown and possibly urgent condition. The case study presented did indeed exhibit asymmetric neuropathy; therefore, an MRI of the head and orbits (emphasis OS) was requested to rule-out compressive orbital disease > OS, ischemic cerebro-vascular disease, as well as evidence of prior demyelinating disease. Carotid Dopplers concentrating on the left side were obtained to explore the possibility of asymmetric vascular insufficiency. Laboratory bloodwork was ordered looking for evidence of vascular inflammatory disease, autoimmune disease, disorders of coagulation or blood dyscrasia, as well as metabolic dysfunction. In the absence of MRI results, the case did not expose related factors other than older age with hypertension and hypercholesterolemia. Therefore, the etiology and pathophysiology of this unilateral presentation is difficult to identify.

The epidemiologic understanding of NTG can be quite complex considering the many multi-factorial associations. Some established causative factors for developing glaucomatous optic neuropathy in normal tension glaucoma are: relatively increased IOP, older age, non-dippers (0-10 %) or extreme dippers (> 20 %) concerning nocturnal arterial blood pressure drop, small vessel disease with cardiovascular disease and cerebral microgliosis (white matter lesions), decreased blood flow in the optic nerve head, extreme dip of the optic nerve head blood flow in the morning, cerebral blood flow dysregulation and the epsilon4-allele polymorphism of the apolipoprotein E-gene.³ Concerning pachymetry, glaucoma patients with thin central corneal thickness are also more likely to be among those with NTG, and the underestimation of intraocular pressure by Goldmann applanation tonometry may possibly be another causative factor.⁴ Regarding poor oxygen perfusion to the ONH, the prevalence of NTG in obstructive sleep apnea syndrome (OSAS) patients has been found to be higher than expected in a white population of the same age; thereby implicating OSAS as a possible important risk factor in NTG as well.⁵ Additionally, it has been shown that the prevalence of vascular risk factors (VRF) is significantly higher in patients with NTG compared to patients with ocular hypertension and glaucoma and that VRF may increase the risk for progression of glaucomatous visual field defects.⁶ In this study, visual field progression was found in 34% of the patients with primary open angle glaucoma (POAG) and indeed found to be significantly higher in 46% of the patients with NTG, with both groups exhibiting VRF.⁶ It is therefore not surprising that a related change in micro-circulation of the optic nerve head may be related to visual field damage in NTG patients but may be less involved in visual field damage in POAG patients.⁷ Regarding functional vs. anatomic outcome variables, circadian fluctuation of mean ocular perfusion pressure (MOPP) was found to be the most consistent clinical risk factor for glaucoma severity in eyes with NTG.⁸ This finding may also suggest an etiology of NTG as a chronic ischemic end organ disease.⁸

As exemplified in the case report, inferior quadrant rim tissue involvement was found to be producing a corresponding superior visual field defect. In NTG, inferior rim blood flow has been shown to be less than superior rim blood flow in patients producing superior hemifield defects, and superior rim blood flow is reduced compared to inferior in patients with inferior hemifield

defects.⁹ Mean superior/inferior (S/I) ratios of mean blood flow (MBF) in patients with superior hemifield defects were significantly higher than in patients with inferior hemifield defects.⁹ Thus, the blood flow in the neuroretinal rim was found to correspond to regional visual field defects in eyes with NTG.⁸ This reduction in flow leading to functional and visual field loss was found to be particularly prevalent with cases of inferior rim deficits producing superior visual field defects.⁹ Perhaps there may be some correlation with gravitational effects producing an inferior “collapse” of the optic nerve and retinal ganglion cells under certain clinical conditions. For these reasons, the inferior rim margin of the ONH must be carefully examined when evaluating the potential NTG patient.

The goal of treatment in the NTG patient is the preservation of optic nerve and RNFL function by inhibiting the progression of glaucomatous optic neuropathy which will ultimately lead to vision loss. Of course, it is accepted that a reduction of intraocular pressure is advantageous and will improve the prognosis in glaucoma patients. However, in addition to IOP, the understanding of ocular and systemic conditions specifically influencing ONH hemodynamics has been found to be most valuable. There have been repeated demonstrations of the importance of ONH hemodynamics and the need for the development of innovative therapeutic technologies.¹⁰⁻¹⁶ This knowledge provides opportunity to recommend supplementary treatment strategies targeting glaucomatous neuropathy from the “back side” rather than purely from an IOP perspective.

Regarding management of the many possible contributing ocular and systemic pathologies discussed previously, calcium channel blockers seem to be the most promising adjunctive treatment to be considered in patients with glaucomatous optic neuropathy without increased intraocular pressure.¹⁷ Calcium channel blockers are a class of drugs that block the entry of calcium into muscle cells including those of arterioles found within the ONH. It is the entry of calcium into these cells that cause the muscle to contract and arterioles to narrow. By blocking the entry of calcium, calcium channel blockers will decrease arteriole contraction allowing for increased perfusion to the optic nerve head thereby enhancing neuro-protection. The calcium channel blocker Nimodipine has been specifically found to increase ONH and choroidal blood flow in NTG patients.¹⁸ In NTG patients with additional vasospastic symptoms, retinal capillary blood is significantly reduced in comparison with healthy controls. Single-dose Nimodipine was also shown to normalize retinal circulation in NTG patients up to values of healthy controls 90 minutes after drug administration.¹⁹

As in the case discussed with NTG and hypertension coexisting, common pathogenetic mechanisms in ciliary and renal tubular epithelia may explain a concurrence of glaucoma and systemic hypertension.²⁰ Therefore, the choice of hypertensive and cardiovascular treatment could substantially influence glaucoma incidence, with beta blockade protecting and ACE inhibitors or calcium channel blockers not affecting underlying risk.²⁰

Hypercholesterolemia and its treatment with the statin drugs Lovastatin and Compactin have been found to also induce changes in cell shape and actin cytoskeletal organization along with other biochemical modifications, all of which are events that are likely to lead to cellular and tissue relaxation.²² Conceivably, this form of cellular reorganization may lead to another level of neuro-protection for the glaucomatous ONH. Another important finding is that statins exert an ocular hypotensive response in an organ-culture perfusion model, indicating the potential for this

class of drugs in glaucoma therapy.²² Therefore, the long-term use of oral statins may be associated with a reduced risk of open-angle glaucoma, particularly among those with cardiovascular and lipid diseases.²³ Nonstatin cholesterol-lowering agents were also associated with a reduced risk of having open-angle glaucoma. Additional investigation is warranted as to whether these classes of agents may provide another therapeutic option for glaucoma.²³

Pharmacological direct neuroprotection is another active area being researched, which in the context of glaucoma, refers to the situation in which a drug is deployed to interact with neuronal or glial elements within the optic nerve head/retina thereby facilitating the survival of retinal ganglion cells (RGC).²⁴ Specific cellular targets have been manipulated with varying degrees of success in relevant animal models including glutamate receptors, autoimmune elements, neurotrophin deprivation, nitric oxide synthesis, oxidative stress products, sodium and calcium channels, heat shock proteins, and apoptotic pathways.²⁴ RGC protection has been discovered utilizing Estrogen hormone therapy which demonstrated a reduction in loss of RGC and neurofibers through the inhibition of ganglion cell apoptosis.²⁵ Moreover, Estrogen therapy yielded a multitude of various positive biochemical cellular events.²⁵ This may be yet another example of a future treatment modality.

Regarding other risk factors and treatment, glaucoma, particularly NTG, has been associated with both high and low blood pressure variations and stroke.²¹ Respiratory disease such as pneumonia and circulatory disorders such as congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) are frequently an underlying causative factor in glaucoma and NTG patients as well.²¹ Treatment of these conditions will allow for increased vascular and oxygen perfusion to the ONH aiding in the prevention of progressive glaucomatous optic neuropathy. Caution must be noted in that the most frequent topical therapy used for glaucoma is the beta-blockers which are contraindicated in COPD and CHF patients. Alternatively, the use of the prostaglandin analogues can not only more safely lower IOP, they have been associated with increased ONH pulsatile blood flow which is of most concern in these cases.¹ Finally, gene therapy focusing on RGC regeneration has been actively researched with hopes of leading to new and novel therapies.²⁶

Conclusion

As evident by the case discussion as well as the examples given of various multi-factorial systemic and ocular contributors, normal tension glaucoma cannot be simply defined. The concerns with etiology, pathogenesis, and pathophysiology of glaucomatous optic neuropathy in NTG are nearly the same as in ocular hypertensive states. Glaucomatous optic neuropathy can be viewed as the inability of the optic nerve and/or retinal nerve fiber layer to maintain integrity and function at any pressure, thereby leading to cupping, excavation, loss of neuroretinal rim tissue, and eventually loss of vision.

True for all glaucoma and particularly normal tension glaucoma, developing a treatment plan based primarily on oculosystemic considerations is a most effective way to provide neuroprotection of the optic nerve leading to preservation of vision. Intraocular pressure must be addressed but only as one part of a bigger picture in the glaucomatous process.

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