# Under pressure: a review of normal-tension glaucoma

# BY DEREK MACDONALD, OD, FAAO

# Introduction

or a disease recognized as a common cause of irreversible vision loss, a universally agreedupon definition of glaucoma remains elusive. Glaucomatous optic neuropathy (GON) is characterized by a progressive loss of retinal ganglion cells (RGC), resulting in an excavated (cupped) optic nerve head and loss of visual field sensitivity.1 Primary open-angle glaucoma (POAG), the most common form of the disease in North America with a prevalence of 2.1%, has been described as "a multifactorial optic neuropathy characterized by acquired loss of retinal ganglion cells and optic nerve atrophy"? This definition has evolved over time, with specific mention of intraocular pressure (IOP) now conspicuously absent. This is at least in part in recognition of the paradox of ocular hypertension (OHT) without accompanying GON, and of GON in the presence of 'normal' IOP; it could be stated that increased IOP is sufficient, although not necessary, for the development of glaucoma. Normal-tension glaucoma (NTG) has been defined as POAG with untreated IOP within the statistically normal range of 15.5 +/-2.6mmHg; others specify that high-water IOP cannot exceed 21mmHg, at which point a diagnosis of POAG is established.<sup>3</sup>

Interestingly, while IOP no longer defines POAG, it does define NTG, and remains the single most important, and the only currently modifiable, risk factor in the development of glaucoma. Further, patients with NTG may demonstrate a more aggressive disease if left untreated, but often respond favourably to IOP-lowering treatment.<sup>4</sup> This has led investigators to suggest that the glaucoma pendulum has swung too far away from IOP, and that the disease may be best defined as the

#### RÉSUMÉ

En moyenne, un patient sur trois atteint de neuropathie optique glaucomateuse aura une pression intraoculaire se situant à l'intérieur des limites de la normale et recevra le diagnostic de glaucome à tension normale. Les professionnels des soins oculovisuels (et leurs patients) auront intérêt à bien connaître le diagnostic, le traitement et le pronostic de cette condition et à bien comprendre non seulement les similitudes et les différences avec le glaucome primaire à angle ouvert mais les rôles importants joués par le système nerveux central et l'état vasculaire systémique.

**Mots clés :** Glaucome à tension normale (GTN), glaucome primaire à angle ouvert (GPAO), hystérèse cornéenne (HC), hémorragie discale (HD), atrophie péripapillaire de la zone bêta (APPβ), pression de perfusion oculaire (PPO), dysrégulation vasculaire, pression du liquide céphalorachidien (PLCR), différence de pression à travers la lame criblée, neuroprotection only *pressure-dependent optic neuropathy.*<sup>5</sup> Indeed, many recommend that the concept of distinct clinical entities be abandoned in favour of viewing glaucoma as a continuum from primarily IOP-dependent (POAG) to IOP-independent (NTG) disease.<sup>6</sup> Given that as many as five of every ten patients with glaucoma will present with statistically normal IOP, an understanding of the multifactorial nature of what this review will term NTG is of critical importance to the eye care practitioner.

# Epidemiology and Risk Factors

Even more than POAG, NTG tends to be a disease of the elderly, with a prevalence of 1.6% in the population over the age of 75; up to 30% of patients with NTG, however, will be under the age of 50.7 Upon diagnosis, the rate of progression and response to treatment appear unrelated to age.8 There is evidence that NTG is more common, more severe, and more resistant to treatment in females.9,10 There also appears to be an ethnic predilection, as upwards of 90% of Japanese and Mongolian patients with POAG present with IOP less than 21mmHg; Caucasians, however, tend to manifest more serious disease.11-13 A family history of glaucoma is reported by 30 to 40% of patients with NTG. Investigators have observed that patients with NTG tend to be of lower body weight and body-mass

index (BMI).14 It has been hypothesized that patients with NTG tend to be more health-conscious (in fact, some would suggest healthanxious), and exhibit more proactive health behaviour. Myopic patients may demonstrate progressive GON in the presence of low IOP, and tend to have difficult to interpret, often tilted, optic nerve heads.15,16 While a discussion of genetics is beyond the scope of this review, upwards of twenty genes associated with POAG have been identified, and there is evidence that several may be specific for NTG. At least two gene loci are associated with NTG and exfoliative glaucoma; these loci influence transforming growth factor beta (TGF- $\beta$ ), perhaps suggesting a future neuroprotective target.<sup>17,18</sup>

# Pathophysiology – Under Pressure

Although by definition NTG presents with IOP within the statistically normal range, admittedly an arbitrary construct with no pathophysiologic meaning, further reducing pressure tends to slow disease progression, albeit not universally.19 Nocturnal IOP elevation, particularly in concert with nocturnal systemic hypotension, is very significant; sleep lab and telemetric studies demonstrate that as many as two out of every three patients exhibit maximal IOP outside regular office hours.<sup>20-22</sup> In recognition of the impact of corneal biomechanical properties on applanation tonometry (AT), and potentially on ocular integrity itself, these properties have recently received greater

attention. Patients with NTG tend to have central corneal thicknesses (CCT) approximately 30 microns below the population mean of 550 microns, leading some to hypothesize that a subset of patients with POAG are misdiagnosed with NTG.<sup>23,24</sup> It has been proposed that the increased prevalence of NTG among some ethnic groups (individuals of Japanese and African descent) may be partly attributable to thin CCT.<sup>25,26</sup> Interestingly, reduced CCT was more common in patients with NTG and vascular dysregulation than in those without, suggesting more than simply an underestimation of IOP.27 While the Ocular Hypertension Treatment Study (OHTS) did lead to fewer patients with OHT and more patients with 'normal' pressures being treated, the association between CCT and glaucoma, specifically whether CCT may be considered a proxy for ONH biomechanical integrity, remains unclear.<sup>28</sup> Recently, the role of corneal hysteresis (CH), reflecting the cornea's viscoelastic ability to dampen fluctuations in IOP and reduce optic nerve head (ONH) strain, has received attention

as another potentially important biomechanical parameter.<sup>29,30</sup> While influenced by CCT, lower CH is consistently and independently associated with an increased risk of GON.<sup>31</sup> There is evidence that a related parameter, corneal resistance factor (CRF, a measure of ocular rigidity), is similarly reduced in cases of concurrently low but fluctuating IOP - that is, NTG.32 Whereas attempts to 'correct' IOP for CCT alone have proven ineffective, 'corneal compensated IOP (IOP)', encompassing a more global corneal biomechanical analysis, may hold promise: IOP<sub>cc</sub> was essentially equal to AT in POAG, but significantly higher in NTG.33 Whether reduced CH and CRF are risk factors for, or a result of glaucoma, and whether they will prove to be better proxies for ONH biomechanical integrity than CCT alone is yet to be determined; further study is necessary.34

Reduced ocular perfusion is found in the majority of patients with glaucoma, more so in the presence of NTG than POAG.<sup>35</sup> Cardiovascular disease, including increased blood viscosity, diabetes,

#### ABSTRACT

On average, every third patient with glaucomatous optic neuropathy will present with intraocular pressure within the statistically normal range, manifesting normal-tension glaucoma. Eye care practitioners (and their patients) will benefit from a familiarity with the diagnosis, treatment, and prognosis of this condition, including similarities to, and differences from, primary open-angle glaucoma, and the important roles played by the central nervous system and systemic vascular status.

**Key words:** normal-tension glaucoma (NTG), primary open-angle glaucoma (POAG), corneal hysteresis (CH), disc hemorrhage (DH), beta-zone peripapillary atrophy (βPPA), ocular perfusion pressure (OPP), vascular dysregulation, cerebrospinal fluid pressure (CSFP), trans-lamina cribrosa pressure differential, neuroprotection

and both systemic hypertension and hypotension, has been identified as a risk factor for the development of glaucoma, and may be predictive of a poor response to treatment.<sup>36,37</sup> In fact, patients tend to show increased risk of glaucoma at both extremes of blood pressure (BP), albeit more so with hypotension, which results in generalized poor perfusion. Hypertension leads to atherosclerosis, damaging endothelial cells and impairing autoregulation, rendering the ONH more susceptible to decreased vascular perfusion, increased IOP, and metabolic demands.38 In the Collaborative Normal-Tension Glaucoma Study (CNTGS), patients without cardiovascular disease tended to progress rapidly when untreated, but benefitted from IOP reduction; vasospastic disease was more predictive of progression than occlusive disease. Magnetic resonance imaging (MRI) of the brain has demonstrated vascular insufficiency in patients with NTG, while cardiac studies have reported an increased incidence of silent myocardial infarction.8,38 In patients with low IOP who show progressive visual field (VF) and ONH damage, systemic hypotension causing low ocular perfusion pressure (OPP, a surrogate being the difference between brachial BP and IOP) may undermine the benefits of low IOP.<sup>39-41</sup> The risk of GON increases as much as six-fold in the presence of low OPP; a diastolic OPP of less than 55mmHg has been associated with a doubling of relative risk.42,43 A physiologic nocturnal BP dip secondary to reduced sympathetic nervous

system activity that coincides with a nocturnal IOP spike can cause a pronounced OPP trough.44,45 Patients with nocturnal BP dips of greater than 10 to 15% demonstrate more significant retinal nerve fiber laver (RNFL) and VF loss.46,47 Some patients may experience iatrogenic systemic hypotension secondary to aggressive treatment of systemic hypertension.48,49 Indeed, aggressive lowering of BP has been shown to increase ONH cupping in patients without glaucoma. Significant variations in OPP, like IOP, may be an independent risk factor for GON and VF deterioration within ten degrees of fixation.<sup>50-52</sup> OPP may be increased by lowering IOP and avoiding overtreatment of systemic hypertension (of course, deliberately elevating BP increases comorbidities), and its variability reduced by smoothing IOP spikes and BP troughs.53

Patients with NTG often have histories of tinnitus, migraine headache, and Raynaud's phenomenon, all manifestations of primary vasospastic vascular dysregulation, an imbalance between autoregulatory vasoconstrictor and vasodilator stimuli.4,14 Patients with migraine, especially women, seem particularly predisposed to rapid (2.6×) progression of NTG, and lowering IOP in women with migraine may be less protective than in those without.<sup>8,12,54</sup> Vasospastic disease is more common in women, particularly post-menopause, and in patients of Japanese descent, two populations known to be at higher risk of NTG. Hemorrhaging within the fingernail

capillary bed, an accepted sign of vascular dysregulation, is statistically more common in patients with glaucoma, particularly in those with a history of disc hemorrhage, and may be a helpful ancillary indication of vascular insufficiency.55 Reduced arterial and peripapillary retinal capillary blood flow has been demonstrated in patients with NTG; many of these patients exhibit vasospastic tendencies and asymmetric VF loss that correlates to interocular asymmetries in blood flow and velocity.56,57 Episodic vasospasm and rebound hyperperfusion can lead to local inflammation and oxidative damage.35 Some patients with presumed GON and statistically normal IOP will have a history of hemodynamic crisis (sudden and severe systemic hypotension); such patients tend to show minimal if any progression over time.<sup>36,37</sup> In fact, in an early study, Drance noted that nearly 90% of patients with NTG had experienced transient or sustained systemic hypoperfusion.<sup>39</sup>

While eye care practitioners routinely measure the trans-corneal pressure differential (the difference between IOP and atmospheric pressure), what truly influences the ONH through disruption of RGC axoplasmic flow is the translamina cribrosa pressure differential (the difference between IOP and orbital cerebrospinal fluid pressure [CSFP]).58,59 The elevated translamina cribrosa pressure differential of POAG caused by high IOP may be mimicked in NTG by a low CSFP within the optic nerve subarachnoid space (ON SAS).60 CSFP

is lower in patients with NTG than in patients with POAG; both groups exhibit lower CSFP than controls (the average being between 5 and 15mmHg), who, in turn, exhibit lower CSFP than patients with OHT.61,62 The inter-group CSFP differences appear similar to the inter-group IOP differences observed in other studies.63 Low CSFP and high trans-lamina cribrosa pressure differential are both positively correlated with GON and glaucomatous VF loss.64 The thinning of the lamina known to occur in GON may exacerbate the trans-laminar pressure differential. Given that pulsatile mechanical stress is more damaging than steady, the role of CSFP fluctuation, akin to IOP fluctuation, is also receiving attention.65 In patients with NTG, the density of CSF in the ON SAS is significantly lower than intracranial CSF; this impairs fluid exchange and leads to relative CSF stagnation within the ON SAS, with potentially detrimental impact upon RGC axons.66 All three pressures (IOP, OPP, and CSFP) are independent yet interrelated, and may be simultaneously influenced by an as yet undetermined systemic mechanism.67 Indeed, one cannot discount the possibility that GON and VF loss attributed to low OPP is actually secondary to low CSFP, as the latter is often found in the presence of systemic hypotension. Neuroimaging has demonstrated a narrower ON SAS width in patients with NTG, suggesting lower CSFP in that space.68 Given that direct CSFP measurement through lumbar puncture (LP) is invasive and not without risk, such a surrogate noninvasive means of assessment would certainly be of value.

# Structural Change

Some investigators feel that NTG exhibits an extreme amount of ONH cupping, typified by a pale, gently sloping, moth-eaten appearance, with broad thinning of the inferior temporal aspect of the neuroretinal rim (NRR).69 Others suggest that the disc changes in NTG represent localized areas of nonperfusion (a focal ischemic glaucoma), preceding or coinciding with adjacent wedge or slit RNFL loss that results in initial severe VF loss that is very close to fixation.<sup>70</sup> This type of damage appears more common in female patients with a history of systemic vasospasm and migraine.<sup>71</sup> Subsequent confocal scanning laser ophthalmoscopic (SLO) studies, however, found no significant differences in optic disc topography in cases of POAG and NTG.<sup>72</sup> The rate of progressive ONH damage may be greater in patients with NTG than in those with POAG, particularly in patients with already-advanced GON, where lowering IOP may be of marginal benefit.73

First described by Bjerrum over a century ago, rising to prominence through the work of Drance some sixty years later, the etiology of disc hemorrhages (DH) remains unclear. Rather than arguing cause versus effect (primary infarction versus secondary degeneration), a mixed-mechanism theory is gaining traction.<sup>74-77</sup> These small pre-laminar radial flame- or splinter-shaped hemorrhages occur most commonly at the inferior temporal aspect of the ONH, adjacent to areas of focal

NRR thinning and RNFL loss, and within two clock hours of areas of beta-zone peripapillary atrophy.78-82 They are two- to five-fold more common in patients with NTG than in those with POAG or OHT, or without glaucoma. Indeed, 15 to 42% of patients with NTG demonstrate DH at baseline or follow-up, versus 7 to 37% of patients with POAG, 8% of those with OHT, and only 0.2 to 0.5% of the non-glaucomatous population.83-88 DH are found frequently in older patients with systemic hypertension, in patients with vasospastic disease, and in women with a history of migraine.<sup>89,90</sup> They are more common in the presence of IOP instability, and relatively rare in patients with secondary OAG, who typically present with significant IOP elevation. In the Early Manifest Glaucoma Trial (EMGT), over half the participants demonstrated DH at least once over an average of eight years; most will be found within the first three to five years of diagnosis.91 However, given that the prevalence of glaucoma is 2 to 4%, up to 70% of isolated DH will be found in patients not (yet) diagnosed with the disease.<sup>83</sup> DH are best detected through photography: being transient and subtle, they are overlooked during clinical exam as often as 84% of the time. Concurrent disease processes, including posterior vitreous detachment, diabetes, or venous occlusion, must be considered in the differential diagnosis.

DH have long been considered a strong and independent risk factor

for progressive GON, increasing the hazard rate by a factor of four to six, more so in patients with NTG than POAG, particularly in elderly patients with pre-existing VF loss.<sup>92-98</sup> In patients with OHT, DH were strong indicators of future conversion to POAG, and were up to five times more common following conversion.94 In the CNTGS, DH was considered a reason to initiate or augment therapy, and was a strong predictor of more rapid progression  $(2.7\times)$  of untreated NTG.99 Up to two-thirds of VF and three-quarters of ONH show progressive change following DH; VF loss may occur at two to eight times the rate, particularly when DH are inferior temporal and/or multiple.74,77,81,90,94,98 Eyes with DH were up to fourteen times more likely to have a worsening of RNFL status within one year. RNFL, NRR, and VF loss can also precede DH by weeks or months; retrospective evaluation has indicated that all eyes developing DH show evidence of preexisting NRR notching.<sup>100</sup> Eyes with enlarging RNFL defects are four times more likely to demonstrate DH, with 80% occurring at the border between unhealthy and healthy RNFL, suggesting that this is the most active anatomical site of glaucoma progression. Such RNFL defects enlarge toward the fovea nearly 90% of the time, causing more central VF change. In light of these relationships, some investigators now consider DH a sign of, rather than a risk factor for, progression.<sup>101</sup> DH become less common in end-stage glaucoma, and then are found nasally, adjacent

to the only remaining viable NRR and peripapillary vasculature.<sup>90,95</sup> Once DH is detected, careful documentation and vigilant follow-up is critical; many investigators suggest every few months, given that the average duration of DH is eight to ten weeks. Recurrent bleeds, often within two years and two clock hours of the initial DH, are found in up to 73% of patients with NTG; eyes that re-bleed tend to have a significantly lower IOP than eyes with isolated DH.76,77,87 A number of studies suggest that patients with recurrent DH have a higher probability of progressive GON, RNFL loss, and more rapid rates of VF deterioration.<sup>102,103</sup> As a rule, patients with DH do not respond as well to treatment as those without.<sup>12</sup> In fact, moderate IOP lowering may not alter the rate of DH, indicating a less IOP-dependent form of glaucoma requiring more aggressive pressure reduction even in the presence of what would otherwise be considered well-controlled IOP<sup>104</sup>

Beta-zone peripapillary atrophy  $(\beta PPA)$  is an absence of RPE and thinning of Bruch's membrane and the choriocapillaris immediately adjacent to the ONH; alpha-zone PPA is pigment irregularity just peripheral to the beta-zone when the latter is present. From a semantic perspective, some argue that the term *parapapillary* is more correct that *peripapillary*, as the atrophy may not completely encircle the ONH. While present in 15 to 20% of normal eyes,  $\beta$ PPA has been noted to be larger and more frequent in eyes with glaucoma, and is considered

an independent, location-specific, and severity-dependent risk factor for the progression of GON.<sup>105-108</sup> Many believe  $\beta$ PPA to be more common in NTG, particularly in younger patients with moderate to severe disease.<sup>109-111</sup> Other investigators feel that  $\beta$ PPA in NTG does not differ from that in POAG, but still helps differentiate NTG from non-glaucomatous optic neuropathy.<sup>112</sup> Nasal  $\beta$ PPA is present in only 1 to 9% of normal eyes, but 15 to 71% of glaucomatous eyes; this may also aid in differential diagnosis.<sup>113-115</sup> Assessing  $\beta$ PPA stability may be particularly valuable in the evaluation of small ONH in which intrapapillary glaucomatous damage can be more difficult to detect.<sup>116</sup> Conversely,  $\beta$ PPA may be less helpful in the evaluation of oblique or highly myopic ONH and in patients of Asian ethnicity, where peripapillary alterations are more prevalent to begin with; ironically, patients with NTG are commonly Asian and/or myopic.<sup>117</sup>  $\beta$ PPA is often found adjacent to an area of focal NRR loss and/or DH, and large areas of  $\beta$ PPA are predictive of future DH. Interestingly,  $\beta$ PPA and DH are associated even in the absence of glaucoma, suggesting a shared etiology of local vascular insufficiency and breakdown of the blood-retina barrier.<sup>115</sup> Some hypothesize that a disturbance of ONH perfusion *secondary* to  $\beta$ PPA may result in sectoral ischemia, or that leakage of vasoactive substances through compromised peripapillary vessels can damage the RNFL in the face of normal IOP.<sup>109</sup> In these cases,  $\beta$ PPA is felt to be a

risk factor for, rather than a sequelae of, glaucoma. That being said,  $\beta$ PPA is not necessarily static; progression can be seen over time, three to five times more commonly in patients with glaucoma, associated with increasing GON and VF loss.<sup>110</sup> The presence and enlargement of βPPA shows significant correlation with RNFL thickness and rate of thinning (particularly in the inferior quadrant), cup/disc ratio, mean VF loss, and NRR area.<sup>114</sup>  $\beta$ PPA shows a strong correlation with VF defects within five degrees of fixation known to be more common in NTG. Both the absolute scotoma of  $\beta$ PPA and the relative scotoma of alpha-zone PPA will cause an enlarged blind spot.  $\beta$ PPA can be detected and monitored qualitatively through ophthalmoscopy and photography, quantitatively through imaging techniques including SLO and optical coherence tomography (OCT).

# **Functional Change**

As already noted, as many as twothirds of cases of NTG present with initial VF defects that threaten fixation; these are strong predictors of future VF deterioration and visual acuity loss.<sup>118</sup> VF defects that threaten fixation are best monitored with both 24- or 30-degree and 10-degree testing strategies. Significant VF deterioration appears to occur in one-sixth to one-third of patients with treated NTG.93 That being said, recall that the CNTGS showed that over half the patients with untreated NTG manifest no discernible deterioration over five to seven years. While conventional

wisdom holds that most cases progress slowly, there is significant variability in rates of progression, even more so than in POAG: a ten-fold range from 0.2 to 2.0dB per year.99 More VF loss is seen in NTG with higher IOP, but IOP variability over both short- and long-term appears to be an important predictor of, and perhaps independent risk factor for, glaucomatous VF progression, particularly in cases of low IOP.<sup>119</sup> The challenge, in both NTG and POAG, is to identify those at risk of rapid progression, and initiate early and aggressive treatment. Particular attention must be paid to localized VF progression, which has been proven to be a strong predictor of future DH, and focal GON.74 It has long been reported that thinning of the RNFL, documented through both qualitative and quantitative means, is an early sign of GON, often preceding VF loss.<sup>120-122</sup> Spectral domain OCT (SD OCT) has indicated that RNFL thinning is most significant at the superior and inferior temporal aspects of the ONH, and correlates strongly with VF deterioration.<sup>123</sup> It has been proposed that loss of 17 to 20% of age-matched average RNFL thickness, to a level of 70 to 75 microns, is the 'tipping point' for structural change, whereas as many as half the RGC may need to be lost to manifest functional (VF) change.<sup>124,125</sup> Given that RNFL thickness assessed through OCT demonstrates a floor effect at approximately 50 microns, it may be best to monitor early GON through structural analysis, but advanced GON through functional

measures.<sup>126</sup> Ideally, a combined index of structure and function would allow better detection, prediction, and follow-up at any stage of the disease continuum than either parameter in isolation.<sup>127</sup>

# Management

Given that IOP remains important in the pathogenesis of NTG, the use of topical anti-glaucoma drugs remains the mainstay of treatment.128 The CNTGS demonstrated that lowering IOP by 30% from baseline, to an average of 11mmHg, reduced the risk of progression nearly three-fold.<sup>19</sup> That being said, 65% of untreated eyes showed no progression over five years of follow-up, while up to 20% of treated eyes did.8 The EMGT, a study in which over 50% of the cohort had NTG, indicated that reducing IOP halved the risk of glaucomatous damage, most significantly in the face of alreadylow pressures.<sup>129,130</sup> The conclusion that each 1mmHg IOP reduction reduced the risk of glaucoma damage by 10% emphasized the importance of vigilant monitoring, and that 'last millimeter of mercury of effect'.107 This aggressiveness must be tempered, however, by the realization that glaucoma treatment is likely to continue for the duration of the patient's life; the side effects of medicine and surgery on quality of life must be carefully considered.131-134 Lowering peak and mean IOP and blunting IOP fluctuation decreases the risk and rate of glaucomatous VF loss.135 While dealing with an admittedly different population, the Advanced Glaucoma

Intervention Study (AGIS) indicated that patients with IOP consistently below 18mmHg demonstrated little if any VF progression over six years; even occasional elevations above 18mmHg resulted in more VF loss.<sup>135</sup> Strict adherence to an individualized and appropriate target IOP appears to result in better VF preservation.132 Particularly with NTG, clinicians must realize that in-office IOP assessment is but a moment in time, and that structural and functional damage may occur exponentially with undetected IOP spikes. This makes the goals of lowering mean and peak IOP, and smoothing short- and long-term fluctuations, equally critical. In the presence of extreme GON, the disease may become essentially pressure-independent, emphasizing the importance of early and effective intervention.

A review of clinical trials indicates that latanoprost, bimatoprost, timolol, and brimonidine are effective in reducing IOP in patients with NTG: latanoprost seems most effective in reducing trough IOP and smoothing the diurnal curve, while brimonidine is most effective in reducing peak IOP, but least effective at trough.136 The World Glaucoma Association recognizes topical carbonic anhydrase inhibitors (CAI) as having a beneficial effect on ONH perfusion through increasing blood flow velocity in the short posterior ciliary arteries (SPCA); prostaglandin analogs (PA) appear to be hemodynamically neutral.137 PA and CAI lower both diurnal and nocturnal IOP, whereas

beta-blockers are ineffective during the nocturnal period. Among the beta-blockers, betaxolol may lower vascular resistance more than timolol, leading to better VF preservation despite higher treated IOP. That being said, should treatment of NTG be initiated, an aggressively low target IOP (approaching episcleral venous pressure of approximately 10mmHg) may be preferable; this target may require multiple medications or the consideration of surgery.19 In addition to traditional topical management, it has been suggested that systemic calcium channel blockers may be protective in cases of NTG through reduction of vasospasm; others argue against their use due to the potential for nocturnal systemic hypotension and reduced OPP.15,44,73,104 Systemic CAI may concurrently lower both IOP and CSFP, leaving the trans-lamina cribrosa pressure differential unchanged, providing little benefit in the management of chronic glaucoma.61

As an adjunct, moderate aerobic exercise may be beneficial in both stabilizing the cardiovascular system and reducing IOP.<sup>138</sup>

Neuroprotection is defined as a therapeutic paradigm for slowing or preventing death of neurons (in the case of glaucoma, RGC and their axons) in order to maintain their physiologic function.<sup>139</sup> Whether secondary to excitotoxic neurotransmitters (glutamate), ischemic/ oxidative injury and subsequent reperfusion inflammation, blockage of growth factors/neurotrophins, mitochondrial dysfunction, or some other mechanism, apoptosis (programmed cell death) may continue independent of the level of IOP.140 Glaucomatous damage is not limited to the ONH; alterations in the visual pathway behind the globe (including lateral geniculate nucleus and visual cortex) have been noted in the absence of detectable RGC loss.141 Given that current treatments are limited to IOP-lowering, yet some patients with glaucoma continue to progress despite low pressures, a treatment that is independent of IOP is certainly enticing. Some current glaucoma medications appear to have neuroprotective activity: in the Low-Pressure Glaucoma Treatment Study (LoGTS), brimonidine demonstrated a beneficial effect on VF preservation independent of IOP-lowering; as previously noted, dorzolamide has been proven to increase OPP.49,137 Memantine and bis(7)-tacrine (glutamate modifiers used in the treatment of Alzheimer's disease, a disease that may share some basic mechanisms of cell death with glaucoma) are among a growing number of systemic agents being studied.142,143

In situations where there are atypical clinical findings (age less than 50, visual acuity less than 20/40, ONH pallor, vertically aligned/neurologic VF defects, lack of correlation between structural and functional change, and/or progression at very low IOP) neuroimaging of patients with NTG to rule out compressive lesions of the optic nerve has been suggested.<sup>16</sup>

# Conclusion

Normal-tension glaucoma is an increasingly common, and certainly challenging, clinical presentation. The challenge begins with differential diagnosis, and continues through follow-up. Practitioners must gather, integrate, and interpret a myriad of data: ophthalmic and systemic, past and present. Given that many untreated patients show little progression over time, careful observation prior to initiating therapy is certainly prudent. That being said, it may be wise to consider more aggressive treatment of NTG in patients with multiple risk factors - for example, a young female with a history of migraine presenting with a disc hemorrhage. While the mainstay of contemporary management remains topical IOP-lowering, the recognition of ocular perfusion and cerebrospinal fluid pressure as important contributing factors may lead to their modification becoming part of the treatment paradigm.

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### Appendix – Illustrative Case Presentation







This case encapsulates the diagnostic dilemma of NTG.

The patient in question is a 51-year old myopic (-7.00D) Asian female who discontinued treatment with prostaglandin analog two years ago. She takes no systemic medications, and denies any symptoms of systemic vascular dysregulation. Her IOPs are 14 and 15mmHg; her CCTs are 494 and 493 microns.

The right ONH (top photo) is obliquely inserted, with superior temporal DH, inferior temporal BPPA, and adjacent RNFL defect. The left ONH shows inferior temporal NRR thinning with adjacent RNFL defect. Initial VF analysis (albeit with questionable reliability; confirmation pending) shows an early superior nasal step in both right and left. Her GP is being consulted to ensure that her systemic vascular status is satisfactory. Pending confirmatory VF analyses, topical treatment with prostaglandin analog (with a target pressure approaching the episcleral venous pressure of ~10mmHg) is likely to be initiated.

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