NORMAL TENSION GLAUCOMA, A CONTINUING CHALLENGE

Ahmad K. Khalil, MD, PhD.


Typical glaucomatous optic disc damage without elevated intraocular pressure was described by von Graefe as early as the middle of the 19th Century\(^1\). Few years later, facing a vigorous opposition to the concept, he abandoned his idea\(^2\). By the middle of the 20th Century, the existence of "low tension glaucoma" had been firmly established. Many authors, however, considered it an uncommon entity, and referred to it as "pseudo-" and "so-called" low-tension glaucoma, with various explanations for the optic disc damage\(^3\), \(^4\), \(^5\), \(^6\). Well into the beginning of 21st Century, normal tension glaucoma remains to be a great source of controversy and challenge in its pathogenesis, clinical characteristics, and optimum management.

The criteria used to define normal tension glaucoma during the last 25 years have been highly variable. However, more recent publications generally require a maximum IOP of 21 mmHg or lower associated with specific features of the glaucomatous optic disc and visual field in the absence of any contributing specific ocular or systemic disorders. The term "low-tension glaucoma" which has been commonly used in the past years, and is sometimes still used, is clearly a misnomer, as the IOP is usually within the normal range rather than being "low".

A different clinical course and the proposition of mechanisms of damage different from those of glaucoma associated with intraocular pressures higher than statistically normal ranges lead many authorities to distinguish normal tension glaucoma as a separate entity. Actually, it is possible that it is a collection of different disease entities. The extent to which it is a pressure-sensitive disease remains to be seen.

Recent scientific advances include elucidation of the genetic mechanism behind the disease and the study of haemodynamic and biochemical co-factors in the development of glaucomatous optic neuropathy, particularly in relation to the pathogenesis of normal tension glaucoma.

**Genetic predisposition and epidemiology**

A genetic component appears to be a factor in the occurrence of normal tension glaucoma. A positive family history of glaucoma is often found in patients with normal tension glaucoma\(^3\), \(^7\), \(^8\), \(^9\). Bennet et al. detected normal tension glaucoma in eight members of a family of consecutive generations, and suggested an autosomal dominant trait for transmission\(^10\).

Normal-tension glaucoma cases are reported to constitute more than 60% of total glaucoma cases in Japan\(^11\). Shiose\(^12\) found 52 cases of high-tension glaucoma and 99 cases of normal-tension glaucoma in a population of 21,820 individuals in Japan. Recently, it has been associated with a Gln368Stop mutation of the GLC1A gene\(^13\). It was noticed to be more severe in men, in an earlier stage of the condition\(^14\).
PATHOGENESIS
The etiology and pathogenesis of normal-tension glaucoma remains surrounded by great controversy. Although elevated intraocular pressure seems to be significant in the pathogenesis of glaucomatous optic neuropathy, increasing evidence suggests both IOP-related and unrelated factors are associated with visual field damage progression in normal tension glaucoma eyes.

Intraocular Pressure
The role of intraocular pressure in the pathological process has been controversial. However, it is generally accepted that IOP is part of the pathogenic process in at least some patients with normal tension glaucoma. In a prospective study, shirai and co-workers showed that the rate of progression was significantly higher in eyes with a mean IOP equal to or higher than 15 mmHg as opposed to eyes with pressures lower than 15 mmHg. Apparently, the functional prognosis in normal tension glaucoma eyes with lower IOP depends on IOP-unrelated factors. A recent study by the Collaborative Normal-Tension Glaucoma Study Group has demonstrated a beneficial role for IOP reduction in hindering progression of the disease, and concluded that intraocular pressure is part of the pathogenic process in normal-tension glaucoma.

VASCULAR FACTORS
Accumulating evidence suggests that a circulatory defect might be a primary factor in the pathogenesis of normal tension glaucoma. Blood flow deficits accompany, and perhaps contribute to, disease development. Hypoperfusion of the optic nerve head might be a significant factor relating to glaucoma damage. It is reported that patients with normal tension glaucoma tend to have blood pressure values lower than normals during both day and night; this difference is probably much smaller than formerly assumed. However, many studies showed that they have significantly greater nocturnal blood pressure drops than normal controls and even those with anterior ischemic optic neuropathy. Abnormal (absence or increased) nocturnal dip of systolic blood pressure was found to be correlated with disease progression in both high and normal tension glaucoma patients. On the other hand, no association between blood pressure or hypertension and normal-tension glaucoma could be found by others.

Increased vascular resistance was found in all retrobulbar arteries in both high and normal tension glaucoma. This points out to the pathognomonic importance of perfusion disturbance in glaucoma. Eyes of patients with normal tension glaucoma with and without progressive visual field defects were shown to have decreased blood flow velocities and increased resistive indices in their retrobulbar arteries, suggesting that differences in ocular blood perfusion are relevant to the development of normal tension glaucoma and are detectable from the early stages of the disease. Furthermore, the finding of lower pulsatile ocular blood flow in normal tension glaucoma eyes with field loss than in the contralateral eyes with normal field suggests that haemodynamic differences between fellow eyes contribute to determine the side of onset of the
disease\textsuperscript{27, 31, 32}. but may be less involved in the deterioration in glaucomatous patients with increased intraocular pressure. The circulatory dynamics of the ophthalmic artery were different in glaucoma patients as compared to normal subjects, and the vascular resistance of the ophthalmic artery may be associated with the development of visual field defects in normal tension glaucoma patients\textsuperscript{33, 34}. Reduced blood-flow velocities of the extraocular vessels in patients with high tension and normal tension primary glaucoma may be secondary as well as contributory to glaucomatous damage\textsuperscript{35, 36}. It was suggested that Vasospasm and generalized cardiovascular disease both appear to be specific risk factors for the development of particular subgroups of glaucoma and may be independent of absolute intraocular pressure levels exerting effects in patients with both "normal" or "raised" intraocular pressure\textsuperscript{37}. The simple assessment as to whether a glaucoma patient suffers from colder extremities than average might point to a focal ischemic type of glaucoma. Patients with normal tension glaucoma were showed to have prolonged arteriovenous retinal passage time, which could cause chronic hypoxia\textsuperscript{38}. They also showed reduced blood flow in the peripapillary retina, a result suggesting that blood flow deficits accompany, and perhaps may contribute to, disease development in these patients\textsuperscript{39}. While optic nerve head ischemia induced by repeated intravitreal injection of endothelin-1 in pigmented rabbits could contribute to the enlargement and excavation of the disk cup independent of the intraocular pressure level\textsuperscript{40}. Decreased erythrocyte deformability was not found to be a major factor in the etiopathogenesis of either normal or high tension glaucoma\textsuperscript{41}.

Other factors
In a study by Jamsen, Six out of 25 normal tension glaucoma patients (24\%) had thyroid disease. In the thyroid group, the mean diurnal IOP variations were significantly smaller. He suggested that thyroid disease either causes optic neuropathy mimicking glaucomatous damage or is a risk factor for glaucoma\textsuperscript{42}. Normal tension glaucoma was also associated with hypothyroidism as a causative factor\textsuperscript{43}. A higher association with one or more immune-related disease(s) as compared with ocular hypertension was found in normal tension glaucoma patients\textsuperscript{44}. Lastly, positivity for immunoproteins such as anti-Ro/SS-A positivity and heat shock protein antibodies in patients with normal tension glaucoma\textsuperscript{45} indicate a possible involvement of an autoimmune mechanism and signify a finding associated with the glaucomatous optic neuropathy process in some patients which appears to be unrelated to intraocular pressure levels.

CLINICAL PRESENTATION
Normal tension glaucoma is a disease often accidentally discovered by the ophthalmologist detecting a suspicious glaucomatous appearance of the optic disc, with subsequent detection of glaucomatous field changes. Less commonly, patients may present with visual disturbances resulting from extensive visual field loss. Because of the subtle onset of damage, and good central visual acuity, the disease is frequently missed. Routine careful examination of the optic disc, therefore, even when glaucoma is not suspected is invaluable for earlier detection of normal tension glaucoma.
Proper assessment of patients includes optic nerve head and retinal nerve-fiber layer assessment, standard static computerized visual field testing, gonioscopy, and a diurnal (24-hours) intraocular pressure evaluation. In addition to a careful history to exclude previous phases of increased intraocular pressure, an internal medicine checkup including 24-hour ambulatory blood pressure measurements and neurological assessment are required. Additionally, carotid artery Doppler sonography, nail fold capillary microscopy, and a computed tomography scan of the brain may prove helpful.

IOP
In most cases, the IOP is at or near the upper end of normal pressure range, i.e.; upper teens rather than lower teens\cite{46}. Some studies have found that the IOP in normal tension glaucoma eyes does not differ significantly from that in the normal population\cite{8}, while others indicate that normal tension glaucoma patients tend to have slightly higher IOPs\cite{47, 48}. Intraocular pressure might increase in normal tension glaucoma eyes following the initial diagnosis. A higher maximum IOP during initial 24-hour pressure curve and the development of disc hemorrhage during follow-up was significantly associated with subsequent IOP elevation in normal tension glaucoma patients\cite{49}. It was suggested that many eyes diagnosed as having normal tension glaucoma have thin corneas, which would tend to lower the tonometrically recorded intraocular pressure compared with patients with primary open-angle glaucoma and normal subjects. This may lead to underestimation of intraocular pressure and misdiagnosis in some of these patients\cite{50, 51}. Another study, however, concluded that for most normal-tension glaucoma patients' corneal thickness is not a major factor in accounting for the lower intraocular pressure measurements when compared with primary open angle glaucoma patients\cite{52}.

Other Glaucoma Parameters
As will be seen in the following paragraphs, great controversy arose as regards the appearance of optic disc and form of cupping, pattern of field changes, peripapillary atrophy in normal tension glaucoma eyes, and weather it is similar to or different from that of high tension glaucoma eyes. These varying opinions probably reflect the different ways in which the 2 entities are detected. Most cases of high tension glaucoma are detected because of an elevated IOP, while most cases of normal tension glaucoma are detected because of optic disc cupping\cite{53}. As it is easier to detect a suspicious IOP than a suspicious optic disc, most cases of normal tension glaucoma are diagnosed at a later stage of the disease process.

Visual Field
A large body of evidence suggests that normal tension glaucoma is different from high tension primary open-angle glaucoma not only in IOP but also in the pattern of the visual field defect, cupping and peripapillary atrophy of the optic nerve head\cite{11}. Many studies noted a difference in the pattern of visual field defects between the two groups. Visual field defects in normal tension glaucoma are noted by many as being relatively more localized\cite{54, 55, 56, 57} and closer to fixation, especially in the supero-nasal quadrant and may be more predominant in the lower hemifield\cite{56, 58}. Another study found that the mean eccentricity of scotomas in normal tension glaucoma was 4.86 degrees from fixation; and 2.96 degrees in high tension glaucoma eyes. These differences were
Koseki et al. detected supero-nasal sectorial damage in normal and not in high tension glaucoma. Another study demonstrated that the upper arcuate area was significantly more depressed in high tension glaucoma and the inferior Bjerrum area was significantly more depressed in normal tension glaucoma eyes. It was also shown that the lower papillo-macular area was less affected in normal tension than in high tension glaucoma eyes. A diffuse-type papillomacular bundle defect was also associated with normal tension glaucoma.

Some earlier studies pointed out that field defects in normal tension glaucoma tend to be deeper with steeper slopes at the edges of the defects. While no statistically significant differences were found between the slopes of the scotomas or depths of the scotomas in the two groups in other studies.

Retinal Nerve Fiber Layer (RNFL)
Early changes in the retinal nerve fiber layer may already exist even in the unaffected area of the visual field in eyes with normal tension glaucoma with hemifield dominant visual field defects. Similar to field changes, much controversy existed as to the damage caused to the RNFL in normal tension glaucoma and high tension glaucoma. Some studies showed that the pattern of RNFL change is different in patients with high- and low-tension glaucoma. Using scanning laser polarimetry, the thickness of the RNFL was found to be reduced symmetrically in the superior and inferior quadrants in high tension glaucoma, whereas a more localized defect on the inferior RNFL occurs in normal tension glaucoma. On the other hand, others denied a significant difference in the frequency of localized RNFL defects between patients with normal tension glaucoma and those with high tension glaucoma.

Disc Hemorrhages
Over the past three decades, hemorrhages on the optic disc have been recognized as a common and significant sign of glaucomatous damage. Several studies confirmed a high prevalence of optic disc hemorrhages in normal tension glaucoma. They are occasionally found on the border or adjacent to the border between the retinal nerve fiber layer defect and the apparently healthy- looking retinal nerve fiber layer and associated closely with the size of peripapillary atrophy. Kitazawa et al. suggested that normal tension glaucoma eyes seem to consist of two different groups; one which develops recurrent disc hemorrhages and one which is very unlikely to bleed through its entire course. The first group probably belongs to the ischemic etiology group as some investigators believe that disc hemorrhages in glaucoma are evidence that ischemia plays a role in causing glaucomatous optic nerve damage.

Optic disc cupping
The appearance of optic disc and form of cupping in normal tension glaucoma eyes, and whether it is similar to or different from that of high tension glaucoma eyes had led to great controversy. Duke-Elder did not recognize any difference in the appearance of optic disc between the 2 groups. In a study by Tezel et al on 394 eyes of 197 patients with high tension glaucoma, and 135 eyes of 68 patients with normal tension glaucoma, the final clinical appearance of optic nerve damage was similar among patients of the 2 groups, and the subgroups of normal tension glaucoma, regardless of their possibly
different mechanisms of neuropathy\textsuperscript{77}. Similarly, no differences were apparent between high and normal tension glaucoma in morphometric parameters of optic nerve head as measured by scanning laser ophthalmoscopy\textsuperscript{78}.

Although some other authors agreed on this similarity, they noted that disproportion between the amount of cupping and the amount of visual field loss is more common in normal tension glaucoma, with larger cup-disc ratios for the same amount of visual loss as compared with high tension glaucoma\textsuperscript{9, 64}.

On the other hand, others\textsuperscript{79, 80} found larger and steeper cups in high tension glaucoma patients, and paler, more sloping cups in normal tension glaucoma eyes. Furthermore, Caprioli and Spaeth found that the optic disc rim in normal tension glaucoma eyes was significantly thinner than in high-tension eyes; the largest difference occurred inferiorly and inferotemporally\textsuperscript{80}.

In one study reviewing the subtypes of normal tension glaucoma, one hundred thirty stereo photographs of optic discs were reviewed in order to identify characteristics of the three following types: focal ischemic, senile sclerotic, and generalized cup enlargement. Twenty patients in each group were selected. Focal ischemic patients were more frequently women, had a higher incidence of migraine, a relatively smaller disc size, and localized superior scotoma that often threatened fixation. Senile sclerotic patients were generally elderly, had a higher incidence of surgery under general anesthesia, more ischemic heart disease or systemic hypertension, a small rim area, and also had extensive peripapillary atrophy as well as combined diffuse and localized visual field defects. Generalized cup enlargement patients were younger, had a relatively larger disc size and a greater incidence of purely diffuse visual field loss. They suggested that the different characteristics of the groups were related to the pathogenic mechanisms specific to each group\textsuperscript{81}.

**Peripapillary atrophy** was significantly associated with functional and structural optic nerve damage in normal tension glaucoma. The area, angular extent and location of zone beta correlated significantly with increasing visual field defects, especially localized defects, optic nerve head topography, and the location of visual field defects\textsuperscript{82}. However, neither zones alpha nor beta differed significantly between normal and high tension glaucoma in either frequency or size\textsuperscript{83}. Similar findings were also made by Tezel et al.\textsuperscript{77}. Funaki, on the other hand, found that the areas of parapapillary avascular area and zone beta in normal tension glaucoma were significantly larger than those in high tension glaucoma\textsuperscript{84}.

**Optic disc size**
Several studies, in recent years, showed significantly larger optic discs in normal tension glaucoma as compared to high tension glaucoma, and suggested that an eye with a large optic disc may be more vulnerable to glaucomatous visual field damage at statistically normal IOP readings\textsuperscript{85, 86, 87, 88}. 


**Systemic associations**

Several systemic associations are noted in relation to normal-tension glaucoma. Patients are said to have more frequent silent myocardial ischemia. The capillary blood-cell velocity in the fingertips was found to be reduced significantly compared with control subjects. Some patients also show evident psychosomatic involvement.

**Differential Diagnosis With Masked High Tension Glaucoma**

Early-morning IOP spikes are one of the important pathogenetic factors in patients with glaucomatous changes without other pathology. Early morning IOP measurement in supine position before rising should therefore be a mandatory part of diurnal IOP curves in patients with presumed normal tension glaucoma. Low scleral rigidity and thin corneas might be misleading in evaluating the IOP. Another possible confusion is damage caused by previous high tension glaucoma, with subsequent lowering of IOP due to hyposecretion of aqueous in a diseased eye.

**MANAGEMENT**

The purpose of a clinical evaluation is to define the most important damaging factors for the individual patient. Accordingly, the therapy is directed towards the possible factors involved. Practically, this can mean: additional lowering of the intraocular pressure, increasing the blood pressure, lowering the blood viscosity and treating the vasospasms. The feasibility of lowering an already low IOP has often been questioned. The literature is full of controversy about optimum treatment protocol for normal tension glaucoma. Achieving sufficient IOP reduction requires topical medication, laser trabeculoplasty, or fistulizing surgery. All of these carry potential risks. As many patients show no progression when untreated, those patients destined to be non-progressive or only slowly progressive would derive no benefit from treatment. Indeed, they would have been exposed to its risks.

A multicenter randomized study by the normal-tension glaucoma study group demonstrated that the rate of visual field progression was significantly less following a 30% intraocular pressure reduction. Some patients, however, remained stable despite receiving no treatment, while others showed a relatively rapid progression. In the meantime, some other eyes demonstrated a rather rapid progression of optic nerve damage and visual field deterioration despite a 30% decrease of IOP. It is evident that at least in some cases, lowering the IOP alone seems not to be the only factor in the outcome of the treatment. In one study dipivefrin had a more favorable outcome on visual field progression as compared to glaucoma despite similar IOP reduction levels.

The favorable effect of intraocular pressure reduction on progression of visual change in normal-tension glaucoma was only found when the impact of cataracts on visual field progression, produced largely by surgery, was removed. Lowering intraocular pressure without producing cataracts is beneficial. Because not all untreated patients progressed, the natural history of normal-tension glaucoma must be considered before embarking on intraocular pressure reduction with therapy apt to exacerbate cataract formation unless normal-tension glaucoma threatens serious visual loss.
Medical Treatment

Beta-blockers

Many of the frequently used ocular hypotensive agents such as beta-blockers and miotics can not produce marked reductions in the IOP which is already in the teen's level. A reduction of only 12% was reported in one study. In a recent alarming study, beta-blocker eye drops were even found to aggravate nocturnal arterial hypotension and reduce the night time heart rate significantly. In normal-tension glaucoma, eyes receiving beta-blocker eye drops showed visual field progression significantly more often than those not receiving beta-blockers. It is also suggested that based on their mechanism of action, the beta-blockers cannot be assumed to reduce IOP during sleep.

A more beneficial effect was demonstrated with the use of selective beta-adrenergic blockade (betaxolol), which was shown to reduce diurnal pressure peaks, a risk factor concerning the maintenance of visual field. It also may have ocular vasorelaxant effects independent of any influence on intraocular pressure, whereas non-selective blockade (timolol) lowers intraocular pressure without apparently altering orbital hemodynamics. Similarly, carteolol hydrochloride was effective in inhibiting deterioration of the local visual field in eyes with normal tension glaucoma. This was attributed to increased ocular perfusion due to diminished intraocular pressure, as well as an inhibitory effect upon vasoconstriction in the optic nerve head due to intrinsic sympathomimetic activity, preventing decrease in papillary blood flow and adverse effects upon ocular circulation.

In recent years, newer agents such as the prostaglandin F2 alpha analogue, latanoprost, has been shown to reduce IOP in normal subjects and ocular hypertensive glaucoma patients by increasing uveoscleral outflow. The magnitude of this IOP reduction was found to be essentially identical during the day and at night. This mechanism should be particularly effective in the lower IOP range that is typical of normal tension glaucoma. Once-daily treatment with 0.005-0.006% latanoprost provides a significant and stable IOP reduction in the majority of patients after short-term treatment. This is accompanied by a significant increase in pulsatile ocular blood flow, and it is well tolerated. It appears to affect ocular perfusion pressure more favorably than timolol does in patients with normal tension glaucoma.

Dorzolamide, a topical carbonic anhydrase inhibitor, significantly reduced IOP at two and four weeks, and at the same time increased contrast sensitivity at both three and six cycles per degree. Dorzolamide also accelerated retinal arteriovenous passage time of fluorescein dye. This ability to improve contrast sensitivity in persons with normal tension glaucoma was related to either IOP reduction or altered ocular perfusion.

Emerging evidence suggests that treatments designed to improve ocular blood flow may benefit glaucoma patients. Ca2+ channel blockade improves contrast sensitivity in patients with normal tension glaucoma and slows the progression of visual field loss. Patients show increased retrobulbar vessel flow velocities, a result supporting that visual function loss may be linked to ocular ischemia. Nilvadipine, a Ca2+ antagonist was found to increase blood velocity and, probably, blood flow in the optic nerve head, choroid, and retina of rabbits. It also increased blood
velocity in the optic nerve head of normal tension glaucoma patients, and reduced vascular resistance in distal retrobulbar arteries in normal-tension glaucoma without affecting more proximal blood vessels\textsuperscript{108, 109}. It also increased Ocular pulse amplitude in vasospastic type normal tension glaucoma patients\textsuperscript{110}.

Similarly, a beneficial effect has been detected for oral brovincamine, a relatively selective cerebral vasodilator in retarding further visual field deterioration in patients with normal tension glaucoma who have low-normal IOP\textsuperscript{111, 112}.

**Surgical Treatment**

Marked pressure reduction can be achieved and maintained on a long-term basis by means other than fistulizing surgery in a large proportion of patients with normal tension glaucoma\textsuperscript{113}. However, surgical lowering of IOP results in a slower rate of visual field loss in the operated eye, and is worth further consideration as a potent treatment for the disease\textsuperscript{11, 114, 115, 116}. The most effective procedure to achieve IOPs of 1 digit (which is believed by many to be necessary to hinder progressive visual field loss)\textsuperscript{9, 117} is probably a trabeculectomy with adjunctive mitomycin C or 5-fluorouracil.

When embarking on treating normal tension glaucoma, the first choice of treatment would be using drugs for reducing IOP and, if necessary, argon laser trabeculoplasty. In addition to these treatments a drug for increasing the blood circulation in the brain can be beneficial in the treatment. Patients whose visual fields are shown by static perimetry to be deteriorating are indicated for filtering surgery.


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