Normal Tension Glaucoma

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Normal tension glaucoma (NTG), also called as low-tension glaucoma, continues to be a diagnostic and therapeutic challenge even in the new millennium.

NTG can be differentiated from primary open angle glaucoma by having an infero-temporally displaced large cup, notching of the neuro-retinal rim in the infero-temporal quadrant, decreased nerve fiber layer (NFL) thickness, flame-shaped disc hemorrhage on temporal side and visual field defects steeper sided & deeper and within five degrees of fixation.

Risk factors for normal tension glaucoma include, females aged 60 years or above, history of peripheral vascular spasm in cold, migrainous headaches and nocturnal systemic hypotension. Ocular examination includes measuring intraocular pressure environment central corneal thickness and paying attention to the optic disc, neuro-retinal rim, NFL thickness & visual fields. Neuro-imaging is required only in specific cases.

Polymorphisms in the OPA1 gene is considered to be a marker for this disease. Careful screening in positive families may detect disease at an earlier stage.

Treatment modalities include differentiating non-progressive from progressive form of normal tension glaucoma. Progressive form requires intra-ocular pressure reduction by 30% by medical or surgical treatment. Betaxolol, latanoprost and dorzolamide are effective as they can increase optic nerve blood flow. Trabeculectomy can be offered when there is progressive visual field loss in spite of intra-ocular pressure being in the lower teens.

The definition of the normal or low tension glaucoma has been a diagnostic dilemma since its original description by Von Graefe in 1857.

In addition to cupping and visual field loss, Duke Elder and Jay included reduced aqueous outflow facility in their definition. Chandler and Grant and Hoskins considered that progression of visual field loss or optic disc cupping as an integral part of the definition. Spaeth and Kolker and Hetherington believed that in normal tension glaucoma optic nerve damage was induced by intraocular pressure, even though the pressure was always within the normal range.

Recently Kamal and Hitchings, putting all puzzles together, have defined normal tension glaucoma with the following criteria.

- A mean IOP equal to or less than 21 mm Hg on diurnal testing, with no pressure spikes greater than 24 mm Hg.
- Glaucomatous cupping of the optic nerve head with corresponding visual field defects.
- Open angles on gonioscopy.
- Absence of any possible contributing ocular or systemic disorder(s).
- Progression of glaucomatous damage.
Normal tension glaucoma has also been regarded as a variant of primary open angle glaucoma. It is also called as “Pseudoglaucoma”, “Posterior glaucoma”, “Paraglaucoma” and “Low tension glaucoma”.

Epidemiology
The prevalence of normal tension glaucoma is not exactly known. In individuals above 40 years of age, its prevalence is 0.2%. It represents 16% to 50% of all cases of primary open angle glaucoma. It is said to be more common in women than men. There is an increased prevalence in female patients with collagen diseases. Of the 153 patients with collagen diseases examined by Yamamoto, Maeda and Sawada et al, 6 patients were found to have normal tension glaucoma and 2 had primary open angle glaucoma. Of these 8 patients, two had progressive systemic sclerosis - out of these two, one was suffering from normal tension glaucoma and the other with primary open angle glaucoma and had a history of systemic steroid therapy.

Normal tension glaucoma usually affects adults, with an average age of 60 years.

Risk factors
It is important to realize that certain factors may affect the incidence and severity of normal tension glaucoma. Many authors believe that their presence significantly increases the risk for developing normal tension glaucoma.

General risk factors
Normal tension glaucoma is said to be more common in people over 60 years of age and is more common in women than men. The disease may run within the family and may be progressive.

(A) Ocular Risk Factors
a. Intraocular pressure:
In most cases of normal tension glaucoma, the intraocular pressures usually cluster at the upper end of the so-called normal range. Many authorities consider intraocular pressure to be an important risk factor for the development of normal tension glaucoma as it is for ocular hypertension. Cartwright and Anderson reported significant amount of cupping and visual field loss in the eye with the higher intraocular pressure. Similarly according to the collaborative normal tension glaucoma study, the level of intraocular pressure does influence the course of normal tension glaucoma. There is a slower rate of incidence visual field loss in cases with 30% or more lowering of intraocular pressure. Some patients experience greater benefit from lowering of intraocular pressure than others.

b. Optic disc hemorrhage
In 1889, Bjerrum is reported to be the first person to describe optic disc hemorrhage and its relation to glaucoma. Since then, many authors have described the prevalence of optic disc hemorrhage in glaucoma.

Optic disc hemorrhage is described in open angle glaucoma, both with high and normal pressures. It is said to be five times more frequent in normal tension glaucoma. Flame-shaped hemorrhages are more common. The usual site is the temporal site of the disc, with the supero-temporal quadrant being more affected than the infero-temporal quadrant. They are usually transient, resolving within four to six weeks. Budde reported that disc hemorrhages are larger in normal tension glaucoma. He observed that smaller hemorrhages in primary open angle glaucoma could be the result of higher intraocular pressure.

Flame-shaped disc hemorrhages are associated with notching of neuro-retinal rim, localized NFL defects and worsening of visual field defects. However these are not specific and can occur in a variety of other conditions including anterior ischemic optic neuropathy, optic disc drusen, posterior vitreous detachment, diabetes mellitus, central and branch retinal vein occlusions, papilloedema, optic neuritis and systemic hypertension. They have also been reported in normal eyes.

C. Peri-papillary defects
These are atrophic changes in the retinal pigment epithelium and chorio-capillaries in the peri-papillary area. They occur with a greater frequency in normal tension glaucoma. Confocal scanning laser ophthalmoscopy and Doppler flowmetry has revealed reduced blood flow in the peri-papillary region in normal tension glaucoma as compared with age matched controls.

Myopia
Myopia occurs more frequently among patients with open angle glaucoma, ocular hypertension and normal tension glaucoma. It is said that congenital misalignment of the peri-papillary tissue layers in myopia, may contribute to the increased vulnerability to pressures even in the normal ranges.
**Systemic Risk Factors**

Among systemic risk factors, the following are more common in normal tension glaucoma than in primary open angle glaucoma.

- Peripheral vascular spasm on exposure to cold (Raynaud’s phenomenon).
- Migraine headaches.
- Nocturnal systemic hypotension and over-treated systemic hypertension.
- Reduced blood flow velocity in the ophthalmic artery, when measured with trans-cranial Doppler ultrasonography.
- Paraproteinemia and the presence of serum auto antibodies.
- Hemodynamic crisis, including myocardial infarction and peri-operative hypotension.

**Patho-Physiology**

Two types of mechanisms are thought to be involved in the pathogenesis of normal tension glaucoma, working either individually or in combination. These are:

a) Pressure-dependant mechanisms
b) Pressure-independent mechanisms

(A) Pressure-Dependant Mechanisms:

Some cases of normal tension glaucoma may not be very different from primary open-angle glaucoma. However in NTG, there is a heightened sensitivity to otherwise normal intraocular pressure.

Intra-ocular pressure tends to be higher in normal tension glaucoma than in the general population. Moreover in normal tension glaucoma, patients with asymmetric intra-ocular pressure, the eye with higher pressure generally has worse optic nerve damage. This concept is also supported by the collaborative normal tension glaucoma study. The study was designed to see the impact of a combination of medical, laser and surgical treatment to produce 30% reduction in intraocular pressure versus no treatment in patients with progressive normal tension glaucoma. The study confirmed that reduction of presenting pressure by 30% slowed the rate of glaucomatous progression in significant number of patients.

Burgeoyne, in the year 2000, demonstrated that certain anatomic features of optic nerve head may increase its susceptibility to a wide range of otherwise normal intra-ocular pressures. Thus the mechanisms of optic nerve damage in normal tension glaucoma may be similar to those, postulated for primary open angle glaucoma; like mechanical and ischemic theories of glaucomatous optic nerve damage.

**Mechanical theory of glaucomatous optic nerve damage**

According to this theory, increased intra-ocular pressure distorts the lamina cribrosa, which then causes compression damage to axons and interfere with axoplasmic flow.

In normal tension glaucoma, there may be local weaknesses of the structural components of the nerve itself. A connective tissue defect at the lamina or in the glial support tissue increases the nerve susceptibility to damage, even in the presence of normal pressures.

**Ischemic theory of glaucomatous optic nerve damage:**

According to this theory, the elevated intra-ocular pressure causes relative ischemia of the optic nerve head that eventually destroys the axons.

Hypo-perfusion of the optic nerve head may play a primary role in the development of the normal tension glaucoma. One-third of normal tension glaucoma patients had a history of previous acute hypotensive episode; e.g. gastro-intestinal or uterine hemorrhage, cardiac arrest, severe anesthetic hypotension, congestive cardiac failure and postural hypotension.

(A) Pressure-Independent Mechanisms:

Corbet demonstrated increased incidence of migraine among patients with normal tension glaucoma, relative to patients with primary open angle glaucoma.

Drance noted that digital blood flow to capillaries in the finger decreased with and without exposure to cold in patients with normal tension glaucoma as compared with controls, while Butt observed increased ophthalmic and central retinal artery resistance while working with colour Doppler imaging techniques.

Various conditions may alter blood flow to the optic nerve head. Drance suggested a non-progressive form of normal tension glaucoma associated with shock or an episode of severe blood loss; while a progressive form associated with vaso-spasm, systemic hypotension and abnormal blood coagulability.
Hayreh demonstrated a greater nocturnal decrease and a lower level of diastolic blood pressure in normal tension glaucoma relative to patients with anterior ischemic optic neuropathy and primary open angle glaucoma.

Thus we can summarize that in normal tension glaucoma, a vascular failure leading to perfusion deficits of the optic nerve head, the retina, the choroids or the retro-bulbar vessels, by means of vaso-sclerosis, small vessel disease, vaso-spasm or auto-regulatory dysfunction may contribute to the optic nerve fibers loss in glaucomatous optic neuropathy.

Clinical Presentation And Investigations

Clinical presentation of normal tension glaucoma is similar to that of primary open angle glaucoma.

It is an insidious disease, which lacks symptoms until central vision is threatened. Ocular examination is the same as with primary open angle glaucoma, with some key distinctions, which are as follows.

Optic Disc Cupping

Normal tension glaucoma tends to have large cupping, with usually infero-temporal displacement of the cup; whereas in primary open angle glaucoma, there is more diffuse cupping.

Heidelberg retinal tomography parameters are useful to differentiate patients with primary open angle glaucoma, normal tension glaucoma and ocular hypertension.

Neuro-Retinal Rim

Notching of the rim is more common in the infero-temporal quadrant of the disc. Scanning laser ophthalmoscopy shows detailed analysis of the neuro-retinal rim, measuring rim area to highlight localized as compared to generalized loss. Digital planimetry gives quantitative assessment even of slight changes of the neuro-retinal rim area, and is a useful tool for follow up of glaucoma patients.

Retinal Nerve Fiber Layer Defect

Heidelberg retinal tomography shows decreased nerve fiber layer thickness. There is a mixture of diffuse retinal nerve fiber layer damage in the supero-temporal and infero-temporal regions. Local damage in infero-temporal region is observed in patients with ocular hypertension and normal tension glaucoma - suggesting that both these glaucomas may follow similar pathological processes.

Disc Hemorrhage

It is five-times more common in normal tension glaucoma than primary open angle glaucoma. Patients with normal tension glaucoma with disc hemorrhage tend to show visual field progression in areas within 10 degrees field.

Peri-Papillary Atrophy

There is higher incidence of peri-papillary atrophy in patients with normal tension glaucoma than the controls.

Visual Field Defects

There is more visual field damage within five degrees of fixation and a high probability of defects in the superior hemi-field in normal tension glaucoma. Superior arcuate defects occur 2 to 4 times more frequent than inferior defects. Moreover, visual field defects tend to be steeper sided and deeper in normal tension glaucoma.

Intra-ocular Pressure

There is a diurnal variation of intraocular pressure, being observed in normal tension glaucoma. Maximum intraocular pressure occurs at 6 a.m., 9 a.m., and at noon and minimum pressure at midnight and at 3 a.m. Thus measuring intraocular pressure in early morning is important for determining the precise diurnal variation of the intra-ocular pressure.

Central Corneal Thickness

It has been observed that central corneal thickness is higher in ocular hypertension, whereas patients with normal tension glaucoma and primary open angle glaucoma showed lower readings.

Thus by determining the central corneal thickness with optical coherence tomography (OCT) - a new and precise technique to measure the central corneal thickness, there is need for a combined measurement of intraocular pressure and central corneal thickness; in order to obtain exact intra-ocular pressure readings.

Polymorphism In Opa1-Gene A - Major Marker For Normal Tension Glaucoma

Normal tension glaucoma is usually diagnosed late, when loss of neurons has already caused significant
and irreversible visual field loss. OPA1-gene (located on chromosome-3), the gene responsible for autosomal dominant optic atrophy, represents an excellent candidate gene for normal tension glaucoma; as the clinical phenotypes are similar and OPA1 is expressed in the retina and optic nerve.

Polymorphism in the OPA1-gene is associated with normal tension glaucoma and is considered a marker for the disease.

Thus careful screening in positive families may detect earlier signs of the disease, allowing commencement of treatment before significant visual field loss has occurred.

Differential Diagnosis
Differential diagnosis constitutes both glaucomatous and non-glaucomatous entities. Conditions causing optic neuropathy and visual field defects and mimicking glaucoma comes into this category.

(A) Glaucomatous Entities
- Undetected primary open angle glaucoma
- Systemic medications, which mask elevated intraocular pressures, e.g. Digoxin, Acetazolamide, Propranolol, etc.
- Pigmentary glaucoma
- Elevated intraocular pressure due to past use of topical or systemic steroids.
- Secondary glaucomas, causing episodic rise of IOP, e.g. uveitic glaucoma

Non-Glaucomatous Entities
- Neurological causes
  - Congenital anomalies
    - Optic nerve pit
    - Optic nerve coloboma
    - Morning glory syndrome
  - Compressive lesions
    - Intra-cranial aneurysms
    - Intra-cranial tumors
- Vascular diseases
  - Prior episodes of shock or anemia
  - Anterior ischemic optic neuropathy

Diagnostic Examination
History

One should inquire about previously raised intraocular pressure, past episodes of visual loss, ocular inflammation or trauma, and use of steroids (both topical and systemic).

History for hypotensive episodes in the past, e.g. associated with severe blood loss, shock and myocardial infarction, atherosclerosis, cerebrovascular disease, temporal arteritis etc, should be inquired.

Nutritional inadequacies, use of digitalis and/or beta-blockers, and history of migrainous headaches should also be recorded.

Ocular Examination
This includes routine external ocular examination and pupillary reflexes. Careful intraocular pressure measurement with applanation tonometer is needed to be checked hourly throughout 24 hours, to assess diurnal variations. Central corneal thickness should be estimated to get an exact IOP reading. Gonioscopy should be done to rule out secondary angle-closure glaucomas.

Optic nerve assessment should be done by careful direct ophthalmoscopy and slit-lamp biomicroscopy. If required, should be supplemented by optic disc stereo-photography with HRT or NFL-analyzer.

Visual field should be recorded with both kinetic and static perimetric techniques. In suspected cases, optic nerve perfusion should be assessed by Ophthalmo-dynamometer.

Medical Evaluation
For every patient, blood pressure monitoring and carotid pulses auscultation should be mandatory. Heart should be screened for cardiac valvular diseases and temporal artery tenderness should be observed.

Complete blood count should be done to rule out anemia. ESR and C-reactive protein should be checked for ruling out giant cell arteritis. Biochemical, coagulation and hematologic testing should be offered in appropriate cases.

All systemic medications having potential for masking raised intra-ocular pressure, e.g. beta-blockers, digitalis – should be discontinued.

Neuro-imaging, like CT or MRI should be advisable in suspected normal tension glaucoma patients where pallor of the neuro-retinal rim appears excessive compared with the degree of cupping.
Patient with normal tension glaucoma should be referred to neurologist or neuro-ophthalmologist, if there is poor glaucomatous correlation between the disc and visual field, and complains of symptoms that cannot be explained by their visual loss.

Management
Management of normal tension glaucoma involves determining progressive nature of the disease.

If the disease is non-progressive, monitoring of visual fields and optic disc is done to establish stability. In this case, monitoring is advised every three months during the first year, then every six months during the second year and then annually thereafter.

If the disease is progressive, the aim of the therapy is to reduce intra-ocular pressure by 30% by whatever mechanisms available.

Medical Treatment
Betaxolol, a selective beta adrenergic blocker, is drug of choice because of its beneficial effects on optic nerve blood flow in addition to its intra-ocular pressure lowering effects. Carteolol hydrochloride is found to be effective by inhibiting deterioration of the local visual field in eyes with normal tension glaucoma.

Prostaglandin analogues, e.g. latanoprost works by increasing uveo-scleral outflow. It appears to affect ocular perfusion more favorably than timolol in patients with normal tension glaucoma. It significantly decreases intraocular pressure throughout the day with no effect on blood pressure and pulse rate. There is 20% reduction of intra-ocular pressure from base-line in patients with normal tension glaucoma.

Dorzolamide, a topical carbonic anhydrase inhibitor improves contrast sensitivity in patients with normal tension glaucoma, related to either intraocular pressure reduction or altered ocular perfusion effects.

0.2% Brimonidine eye drops – an alpha-2 adrenoceptor agonist, can induce a significant intraocular pressure decrease in eyes with normal tension glaucoma.

Systemic calcium channel blockers, e.g. Nifedipine, can be considered in young patients and in those with early disease. They improve blood flow in the optic nerve head by inhibiting constriction of smooth muscles in the vessels, and reduce vascular resistance in distal retro-bulbar arteries in normal tension glaucoma without affecting the more proximal blood vessels.

Monitoring of systemic blood pressure for 24 hours period is advisable. If a significant nocturnal drop is detected, it may be necessary to avoid anti-hypertensive medications, especially if taken prior to bed time.

Surgical Treatment
Trabeculectomy in normal tension glaucoma is required, if progressive visual field loss occurs despite intra-ocular pressure being in lower teens.

Adjunctive anti-proliferatives in normal tension glaucoma may be required. The use of Mitomycin-C is associated with a greater risk of visual field defect progression, despite a greater fall in IOP. The use of adjunctive peri-operative 5-FU should maintain a suitable target intraocular pressure with preservation of visual functions, without additional complications & associated visual field deterioration as seen with adjunctive Mitomycin-C.

Recently there has been emphasis on the use of neuro-protective drugs that may act independently of the effect of lowering the intra-ocular pressure. No data are yet available which can demonstrate that treatment with neuro-protective agents will indeed result in long-term preservation of visual fields.

Summarizing, patients with normal tension glaucoma benefit from lowering of intra-ocular pressure. The treatment should be individualized according to the stage of disease and rate of progression. Trials are on their way that will help predict risk and the rate of progression and response to treatment; and when fully known, will help in treating patients with normal tension glaucoma.

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