NEW FRONTIERS IN THE TREATMENT OF NORMAL TENSION GLAUCOMA

Ahmad A*, Akhtar N**, Abdul Waris**
Institute of Ophthalmology, A.M.U, Aligarh- 202002, India

ABSTRACT:

Normal Tension Glaucoma (NTG) is labelled when typical glaucomatous disc changes, visual field defects and open anterior chamber angles are associated with intraocular pressure (IOP) constantly below 21mm hg. Chronic low vascular perfusion and Raynaud's phenomenon are the main causes of normal tension glaucoma.

Treatment is generally aimed at lowering IOP by 30 % from pre – existing levels to 12-14 mm hg.

Studies now show that the choice of medication may also be important in determining the outcome for the patients. The present review summarizes the treatment of NTG.

KEYWORDS:

Normal Tension Glaucoma (NTG), Neuroprotection, Intraocular pressure(IOP), Glaucomatous Optic Neuropathy (GON)

INTRODUCTION:

Glaucoma is a progressive optic neuropathy that causes characteristic optic nerve and visual field changes in relation to IOP.[1] It is now known that glaucoma can occur at statistically normal IOP and prevalence studies have shown NTG to be more common than previously thought.

Both glaucoma phenotypes have normal anterior chamber angles, peripapillary retinal nerve fiber layer (RNFL) thinning, GON, and corresponding visual field (VF) defects[2,3]. Because of these similarities, it has been postulated that NTG and high-pressure POAG represent a continuum of open-angle glaucomas and differ basically in the importance of IOP on the development and progression of the disease[4]. Therefore, it is crucial to define glaucoma based on the characteristics of the optic nerve and not to use a single risk factor, IOP, to distinguish among the various conditions of GON.[2]

Visual field defects in NTG are essentially comparable to POAG. In general, patients with NTG appear to have deeper, more localized scotomas[4],a difference in the progression pattern as compared to POAG patients; in POAG eyes, field defects initially increased in area and later in depth, whereas in patients with NTG, the increases in area and depth remained in constant proportion.[5]

Investigations include 24-hour blood pressure monitoring to exclude nocturnal systemic hypotension; blood tests to rule out other causes of glaucomatous optic neuropathy such as vitamin B12 and

*Junior Resident, Institute of Ophthalmology A.M.U., Aligarh, India
**Assistant Professor, Institute of Ophthalmology A.M.U., Aligarh, India

folate levels, ESR/CRP and serum ACE. Cranial MRI may be necessary to rule out intracranial space occupying lesions (SOLs); and nail fold capillaroscopy with cold provocation may detect blood flow abnormalities.[6]

Pathogenesis

The pathogenesis of NTG is unclear, and perhaps the development of the disease is a consequence of a complex interaction of several systemic and ocular factors. Different studies have shown that the cardiovascular system and intracranial pressure may be involved in the main pathways of optic nerve damage. Nevertheless, the complex relationship between these mechanisms and glaucoma progression continues to be debated.

DIAGNOSIS AND EVALUATION

Diagnostic evaluation of NTG should always begin with thorough medical history and review of systems. It is not uncommon for such patients to communicate a history of cold extremities, migraine headaches, systemic hypotension, or other signs of vascular dysregulation.[7-8]

A systemic evaluation of potentially contributing conditions, such as Obstructive Sleep Apnoea (OSA) or Raynaud's phenomenon, is often significant in cases of disease progression refractory to IOP lowering therapy. The diagnosis of NTG can even be diagnostic in some patients who were previously unaware of the presence of contributing systemic disease. Since NTG is a disease entity in which non ocular systemic abnormalities are believed to play a significant role in disease progression, optimization of potential IOP – independent factors can be helpful in slowing the progression of eye disease. When the rate of disease progression remains unchanged despite optimization of both IOP and IOP- independent risk factors, the diagnosis of NTG should be re-evaluated and a work-up for non-glaucomatous causes of vision loss should be considered.

TREATMENT:

The mainstream treatment for NTG is IOP reduction. The Collaborative Normal-Tension Glaucoma Study demonstrated that a 30% IOP reduction favorably influenced the progression of this disease in glaucoma patients compared with untreated NTG controls. The favorable effect of IOP reduction in the treated group was found only when the impact of cataracts on VF progression was nullified. Moreover, in the same study, even after achieving the expected IOP reduction, the disease continued to progress in 12% of patients[9-10].

The most frequently prescribed antiglaucoma drugs used in monotherapy in several studies did not reach the pressure reduction suggested by the Collaborative Normal-Tension Glaucoma Study. Prostaglandin analogues (latanoprost and bimatoprost), beta-blockers, and alpha-adrenergic agonists reduced the pressure from 16% to 20% when used in monotherapy[11-12]. Among fixed combinations of drugs, the dorzolamide-timolol compound reduced 23.7% of baseline IOP, and combined brimonidine-timolol drops lowered IOP by 3.8 mmHg (23%) after 12 weeks of use in NTG patients[13-14].

The Low-pressure Glaucoma Treatment Study compared the effects of brimonidine and timolol in monotherapy for NTG. Brimonidine-treated patients were less likely to have VF progression despite known comparable IOP decreases[15]. Hayreh *et al.* suggested that topical beta-blocker eye drops induce a significant drop in mean diastolic BP at night and that beta-blocker-treated NTG patients showed VF damage progression more frequently than those not receiving this class of eye drops[16].

Extracts of *Ginkgo biloba* have been suggested for many years to treat various conditions,

particularly circulatory problems, Alzheimer's and other age-associated dementias, cerebral blood insufficiency, and schizophrenia[17]. Several studies have been conducted to test its potential as a neuroprotective and antioxidative drug and to understand the possible benefits in the management of neurological and vascular conditions[18]. Lee *et al.* reported that a prolonged (72.1 ± 16.4 months) administration of *G. biloba* slowed the progression of VF damage in patients with NTG, particularly in the superior central region[19].

Furthermore, several drugs that act on ocular blood flow have been tested. Calcium channel blockers, such as nimodipine, normalized the retinal blood flow in NTG patients with vasospasticsymptoms[20] and increased the blood and choroidal flow[21]. However, its potential benefits must be validated in randomized clinical trials.

Unoprostone is another drug with potential neuroprotective properties in pre-clinical studies. Unoprostone is a prostanoid and synthetic docasanoid that is approved by the United States Food and Drug Administration for IOP reduction in OAG and ocular hypertension through increased aqueous outflow via the trabecular meshwork. Recent studies suggest that unoprostone may prolong neuronal survival independent of its ability to lower IOP, in part due to improved ocular blood flow via antagonism of ET-1.[22,23]

Glaucoma filtering surgery is indicated when adequate control cannot be achieved with medical therapy or laser trabeculoplasty. Because the target IOP is often lower in NTG than in POAG, NTG patients are at greater risk for ocular hypotony and related complications, such as hypotonymaculopathy, post-operatively.

Aqueous shunts are another surgical option which have become increasingly popular in the past decade and especially so after the recent Tube Versus Trabeculectomy (TVT) study. It should be noted that the TVT study did not demonstrate superiority of tube shunts over trabeculectomy as primary glaucoma surgery and such a trial is currently in progress.More recently, the concept of "non-penetrating" glaucoma surgery has gained interest for its potential to limit some of the complications associated with more invasive procedures to lower IOP.

Subsequent prospective studies comparing non-penetrating deep sclerectomy directly with trabeculectomy have shown similar IOP-lowering results with improved complication rates,[24,25,26,27] suggesting that such less invasive surgical procedures may have an increasing role in the treatment of NTG and other forms of glaucoma.

CONCLUSION

The complex etiology of NTG is not yet completely understood; however, several studies presented differences between this disorder and high- pressure POAG . In clinical practice, the adequate reduction of IOP remains the keystone for managing NTG patients. Some alternative treatments must be tested further in randomized clinical trials to verify their therapeutic effects.

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