Approach to the Management of Normal Tension Glaucoma as a Glaucoma Surgeon

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ABSTRACT

Normal tension glaucoma (NTG) is an open angle glaucoma characterized by normal intraocular pressure (IOP) levels, open angle and slowly progressing glaucomatous optic neuropathy. Although IOP independent risk factors, such as vascular dysregulation are believed to play an important part in the etiopathogenesis, IOP reduction is still the mainstay of treatment in NTG. IOP lowering therapy consist of medical, laser and surgical treatment. The glaucoma surgical options are indicated when medical and laser therapy are unable to reach targeted pressure. The approach to management of normal tension glaucoma as a glaucoma surgeon is discussed in this review.

Keywords: Normal tension glaucoma, Glaucoma surgical treatment.

INTRODUCTION

Normal tension glaucoma (NTG) is a primary open-angle glaucoma (POAG) characterized by development of glaucoma-specific structural and functional damage at optic nerve head and visual field despite intraocular pressure (IOP) ≤21 mmHg throughout a day. European Glaucoma Society (EGS) warrants IOP within diurnal normal range and presence of progressive glaucomatous damage at optic nerve and visual field together with lack of any other cause that may result in glaucomatous optic neuropathy for diagnosis.[1] The conditions that cause optic disc pitting with normal IOP may be confused with NTG. Primarily, these conditions include undiagnosed high-tension glaucoma (HTG) and neuroophthalmic disorders.[2, 3]

The NTG prevalence is estimated as 0.2% among individuals aged >40 years in USA, accounting for 20-40% of patients with POAG.[4] In Asian population, it is higher and accounts for 90% of patients with POAG.[5, 6] The risk factors include advanced age, female gender, some racial characteristics (more common in Japan population), family history, thinner central corneal thickness (CCT), splinter hemorrhage at optic disc, Raynaud's phenomenon, migraine and sleep-apnea syndrome.[1, 3]

In NTG, it is predicted that axons are injured even at lower pressures due to increased susceptibility of optic head nerve despite IOP within normal range.[3] This is explained by role of factors other than IOP in the pathogenesis of NTG.[7] These include ocular and systemic vascular disorders, immune mechanisms, ganglion cell excitotoxicity and increased translaminar stress due to low cerebrospinal pressure among others.[3-7]

Distinctive Clinical Features in Normal-Tension Glaucoma

Besides different IOP measurements, there are some clinical features that distinguish normal-tension glaucoma from high-tension glaucoma. In eyes with NTG, there is thinner CCT and lower hysteresis, larger optic disc, wider optic pit, thinner neuroretinal rim and wider ß-zone peripapillary atrophy. The damage in optic nerve head causes focal notching at neural rim, lower temporal segment in particular. In NTG, the optic disc hemorrhage rate is 2 to 5 folds higher than high-tension glaucoma.[3]

In NTG, visual defects are more localized, close to fixation point with steeper and deeper margins. In particular, they tend to appear as isolated paracentral defects at upper one-half of horizontal line.[3]

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In normal-tension glaucoma, it has been reported that large diurnal IOP fluctuations are seen with frequent nocturnal and postural peaks.[8] It was reported that IOP elevation at supine position is a risk factor for progression.[9,10] In NTG, female gender, migraine and disc hemorrhage are considered as risk factors for progression.[11,12]

In this type of glaucoma which is known to have slow progression rate and no progression in one-half of cases even without treatment, treatment should be started in conditions where visual field defects threaten fixation point and in case of disc hemorrhage or thinning in peripapillary retinal nerve fiber layer (RNFL) suggestive of progression.[1,3,11-14]

Treatment in Normal-Tension Glaucoma

Based on available studies and evidence-based data, IOP lowering treatment is the single treatment modality proven to be beneficial in slowing progression. Neuroprotective treatment hasn't been proved to be beneficial.[1,3,12] Collaborative Normal-Tension Glaucoma Study (CNTGS) is the pivotal multi-center, randomized, controlled trial on treatment of NTG.[13] In the study, it was shown that IOP reduction by 30% decreased progression rate from 35% to 12% at year 5.[13] However, the IOP reduction could not prevent progression in all patients. This does not necessarily mean that IOP reduction is futile.[11] In Early Manifest Glaucoma Trial (EMGT), it was reported that the extent of IOP is directly proportional to prevention of progression in patients with NTG.[14] In other studies, it was supported that visual field progression could be prevented in greater extent when greater reduction was achieved in IOP by medical treatment or trabeculectomy.[15,16] These findings suggest that lower pressures should be aimed and treatment should be re-planned in accordance to the treatment target in patients with persistent progression despite IOP lowering therapy.

In normal-tension glaucoma, IOP lowering therapy is similar to POAG; stepwise approach should be adopted as medical, laser and surgical therapy.[1] Prostaglandin analogs (PG), beta-blockers, alpha-2 agonists, carbonic anhydrase inhibitors and miotic agents can be used as hypotensive agents.[1,3,12] However, it is known that anti-glaucomatous agents are less effective in this type of glaucoma with normal IOP when compared to high-tension glaucoma.[12] Although prostaglandin analogs may be first-line treatment, there are studies reporting that, by 20% reduction in IOP, they are inadequate in treatment.[3]

In beta-blockers, there may be adverse effects on visual field by decreasing blood flow to optic nerve head due to potential systemic side effects such as hypotension and bradycardia.[3,17] Krupin et al. found that the progression in visual field was markedly less in NTG patients on brimonidine therapy than those on timolol maleate despite similar IOP lowering effects (9.1% vs. 39.2%).[18] In the study, authors emphasized potential neuroprotective effects of alpha-2 agonists and potential neurodestructive effects of beta-blockers. Despite proven favorable effects of alpha-2 agonists on visual field, long-term intolerance due to marked adverse effects and poor diurnal control on IOP limit their use.[3,18] In carbonic anhydrase inhibitors, 17% IOP reduction is insufficient for their use as a single agent. Currently, miotic agents are less commonly preferred due to higher rates of adverse effects.

In NTG, IOP lowering therapy is similar to those in POAG with stepwise approach using medical therapy, laser and surgery.[1] Prostaglandin analogs (PGAs), beta-blockers, alpha-2 agonists, carbonic anhydrase inhibitors and miotic agents can be used as hypotensive agents.[1,3,12] However, it is known that anti-glaucomatous agents are less effective in this type of glaucoma with a normal range of IOP when compared to high-tension glaucoma.[12] Although prostaglandin analogs are first-line treatment in NTG, there are studies reporting that 20% IOP reduction by PGs is inadequate for treatment.[3] Beta-blockers may have unfavorable effects of visual field by reducing blood flow to optic nerve head due to their systemic adverse effects such as systemic hypotension and bradycardia.[3,17] Krupin et al. found that, despite comparable IOP lowering effects, visual field progression was markedly lower in NTG patients treated with brimonidine than those treated with timolol maleate (9.1% vs. 39.2%).[18] Authors indicate potential neuroprotective effects of alpha-2 agonists as well as potential neurodestructive effects of beta-blockers. Despite favorable effects of visual field, poor long-term intolerance due to marked side effects and poor diurnal control limits use of alpha-2 agonists in NTG.[3,18] The IOP reduction by 17% achieved with carbonic anhydrase inhibitors is inadequate for use as single agents. Currently, miotic agents are less commonly preferred due to higher rate of side effects. Combination therapy should be considered when monotherapy failed to achieve IOP reduction by 30%.[1,3]

In normal-tension glaucoma, it is difficult to achieve target pressure by medical treatment alone since IOP is within normal range. In EMGT, it was reported that argon laser trabeculoplasty (ALT) plus beta-blocker (betaxolol) combination resulted in marked reduction in IOP in patients with IOP<15 mmHg, proposing that ALT has limited effect in this type of glaucoma.[14] In the literature, there are studies reporting that selective laser trabeculoplasty (SLT) is associated with better diurnal IOP control when compared to medical treatment.[19] SLT can be employed when medical treatment fails or contraindicated. However,

it should be kept in mind that IOP lowering effect is as much as PG analogs in SLT.[20]

In CNTGS, it was reported that medical treatment and laser therapy failed to achieve target IOP (reduction by 30%) in approximately one-half of patients and surgical treatment was performed in 43% of cases.[13] In the study, beta-blocker and adrenergic agents were not used due to potential cardiovascular effects. Target IOP could be achieved in many patients by other anti-glaucomatous eye drops and laser therapy. However, surgery was required to reduce pressure below episcleral venous pressure in patients with ongoing progression in visual field despite IOP ranging at levels of 10 mmHg. In these patients, trabeculectomy was performed as glaucoma surgery.[13]

Trabeculectomy is the most intensively studies surgical intervention as it is current gold standard for glaucoma surgery. In a study on NTG patients from Japan, it was reported that 38% IOP reduction was achieved by trabeculectomy and that visual field progression was less common in surgery group when compared to medical treatment group.[19] In many other studies, it was found that progression in visual field was prevented by achieving target IOP via trabeculectomy surgery.[16,21-23] In a recent study, IOP fluctuations during reading and writing activities on smart phone were studied in 78 NTG patients treated with medical or surgical (trabeculectomy) interventions. It was found that IOP fluctuations were markedly lower in patients treated with surgery compared to those on medical treatment.[24]

In NTG, minimum 25% reduction must be achieved for satisfactory decrease in IOP within normal range, which sometimes corresponds to IOP at units digit.[25] This is associated with risk for hypotonia. In addition, trabeculectomy should be combined with anti-metabolites to achieve IOP at units digit. The risk for ocular hypotonia secondary to avascular blebs with leakage and extremely low IOP targets drives clinicians to safer surgical options. In a study by Aihara et al., it was reported that a satisfactory reduction in IOP from 10.0±3.1 mmHg to 4.8±2.3 mmHg was achieved via EX-PRESS mini shunt surgery in 37 eyes with NTG. Authors proposed that this surgery in which no serious complication was observed may be a safe alternative to trabeculectomy.[26]

Aqueous shunts has become a more popular surgical option in last decade, particularly following tube vs. trabeculectomy (TVT) study.[27] The TVT study compared outcomes and complications between trabeculectomy and Baerveldt-350 implant surgery in eyes with previous history of glaucoma or cataract surgery.[28] At the end of year 5, it was found that aqueous shunt surgery was associated with lower failure rate and less complications when compared to trabeculectomy in eyes with history of previous surgery; however, it was failed to demonstrate superiority of aqueous shunts to trabeculectomy when employed as primary surgery.[28] In a similar study comparing trabeculectomy and Ahmed glaucoma valve, it was found that, at the end of year 5, trabeculectomy was more successful in fulfilling predefined success criteria as IOP≤18 mmHg and IOP reduction by ≥20%.[29] In conclusion, it can be suggested that trabeculectomy is more appropriate surgical option than glaucoma drainage devices in NTG.

In recent years, the concept of non-penetrating glaucoma surgery (NPGS) has gained interest due to its limited complication rate when compared to invasive surgeries.[27] Deep sclerotomy in which inner wall of Schlemm canal is peeled without access to anterior chamber is primary example for these surgeries. Lachkar et al. reported 33.8% IOP reduction with minimal complication at the end of year 6 after deep sclerotomy.[30] In a meta-analysis comparing NPGS and trabeculectomy, it was concluded that trabeculectomy is successful in achieving IOP reduction while complication rate is significantly lower with NPGS.[31]

CONCLUSION

Normal-tension glaucoma is a type of POAG, which has specific clinical characteristics and challenges in the treatment. Although many factors such as ocular and systemic dysregulation play role in the pathogenesis, IOP lowering therapy is the only treatment modality proven to beneficial in NTG as it is the case in other types of glaucoma. In multicenter, randomized, controlled studies, it was shown that IOP reduction by 25-30% decelerates progression in visual field and even it decreases progression by 50%. It was also reported that additional IOP reductions (particularly <10 mmHg) are beneficial to prevent progression in cases with persistent progression despite 30% IOP reduction. It is more feasible to achieve such IOP target at units digit. Trabeculectomy is the most commonly preferred surgical method while alternative methods include shunt tube and non-penetrating glaucoma surgeries.

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