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Research Article

Updates on Normal Tension Glaucoma Management

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Abstract

Purpose: To review the recent publications and updates on the treatment of normal tension glaucoma (NTG).

Design: Systematic review.

Methods: Relevant publications were identified in Medline, Scopus, Embase and Cochrane using the keywords. Results were reviewed, tabulated and summarized.

Results: The literature focuses on prostaglandin analogues as the first line of treatment in NTG. However, there are several reports on the use of beta blockers, α2 agonists and combination drugs. Fifteen papers reporting the outcome of surgical treatment of NTG met our inclusion criteria. There is an increasing trend toward the use of neuroprotective agents to stop the progressive glaucomatous damage in NTG. Five papers were identified reporting the role of neuroprotection in this type of glaucoma.

Conclusion: The present review summarizes the treatment options for patients with NTG. Medical treatment remains the first choice. However, there are several surgical options that can be considered in refractory cases that require further intraocular pressure (IOP) reduction. Neuroprotection is an interesting field of research in NTG that might offer new hopes to overcome this debilitating condition in the future.

Keywords: Glaucoma; Prostaglandin; Neuroprotection

Introduction

Normal tension glaucoma (NTG) is a type of open-angle glaucoma with typical glaucomatous optic nerve head damage, characteristic visual field defects, progressive changes on follow-up examinations and maximum intraocular pressure (IOP) less than 21mmHg [1]. Risk factors of NTG include: 1: Older age; 2: Female gender; 3: East Asian ethnicity; 4: Low central corneal thickness [2]. Moreover, signs of vascular dysregulation (such as cold hands and feet, migraine headache and systemic hypertension or hypotension) are more likely to be found in patients with NTG. Other pertinent findings may include a history of sleep apnea or arterial obstructive disease [2]. Flammer syndrome is a recently described clinical condition. Patients with this clinical entity may suffer from a group of symptoms, which are related to blood flow dysregulation such as cold hands and/ or feet, increased sensitivity to pain, decreased sensation of thirst, migraine and tinnitus [3]. It is found that impaired blood flow to the optic nerve head and normal tension glaucoma is more common in patients with Flammer syndrome [4].

Goldman applanation tonometry, stereoscopic biomicroscopy of optic nerve head, gonioscopy, optical coherence tomography and visual field analysis are essential for diagnosis of NTG. Early diagnosis of NTG is of paramount importance due to its lack of symptoms until advanced stages [2].

Until now, IOP remains the only modifiable risk factor for the treatment of glaucoma. Although NTG is defined by an IOP that is in the normal range, IOP still plays an important role in the pathogenesis of NTG, and lowering IOP is effective in slowing the progression of glaucomatous damage [2]. Results of Early Manifest Glaucoma Trial revealed that glaucoma progression was decreased by 10% with each mmHg reduction in IOP [5]. Collaborative Normal Tension Glaucoma Study showed that IOP reduction of 30% slows the progression of NTG [6]. Several hypotensive medications have become available in the market in recent years. Previous studies have shown that prostaglandin analogues are the effective agents for lowering IOP in NTG patients, with mean IOP reduction of 20% [7]. Timolol has the same efficacy, although it may have greater IOP reduction at trough than at peak [8]. Surgical intervention is the next line of treatment should the maximum medical therapy fails to slow the progression. Recently, the role of neuroprotective agents is highlighted in prevention of retinal ganglion cell (RGC) loss.

In this paper, we aim to review the most recent publications regarding the treatment of NTG.

Methods

We searched four databases including Medline, Scopus, Embase and Cochrane for these keywords; "NTG", "normal tension", "normal pressure", "low tension", "low pressure", "treat*", "therap*", "medication" and "manag*". Search results were confined to papers published from 2011 to 2017. 1162 articles identified in the preliminary search, and 505 items were duplicates. Remaining 657 papers underwent primary screen for relevant subjects and 301 items were chosen. Abstracts were studied carefully, and 60 articles were selected for full-text evaluation and conducting a review. The final selection was rechecked by another reviewer to prevent any missing or improper selection. We included only papers with full-text or

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Table 1: Published papers on medical therapy in NTG.

Author/Year	Study design	No. of cases	F/u (m)	Findings/outcome
Feke et al. 2014 [9]	Non-randomized clinical trial	46 patients	2	Brimonidine improves retinal vascular dysregulation in NTG patients
Tsumura et al. 2014 [10]	Prospective multi-center study	75 patients	3	The addition of 0.1% brimonidine tartrate preserved with sodium chlorite to on-treatment NTG patients with IOP ranging 13-16mmHg further reduces IOP with minimal adverse effects
Araie et al. 2012 [11]	Multi-center prospective RCT	146 eyes	36	1 mmHg IOP reduction over 3-year period in NTG patients under treatment with Beta blocker
Kim et al. 2016 [12]	Multi-center RCT	110 patients	3	Brimonidine/Timolol fixed combination has a superior effect on lowering the IOP
Kim et al. 2013 [13]	RCT	37 patients	3	Dorzolamide/Timolol fixed combination is a safe and effective drug to decrease IOP
Lee et al. 2016 [14]	Interventional prospective study	44 patients	1	Dorzolamide/Timolol fixed combination can be used safely in NTG patients with minimal effect on ocular perfusion pressure
Lee et al. 2016 [15]	Interventional prospective study	44 patients	3	The effect of Dorzolamide/Timolol fixed combination is comparable to latanoprost
Mizoguchi et al. 2011 [16]	Multi-center RCT	40 patients	2	Adding dorzolomide/timolol fixed combination to prostaglandin analogues can produce further IOP lowering effect
Mizoue et al. 2017 [17]	Multi-center RCT	128 patients	3	Brimonidine results in further reduction of IOP in patients already receiving a prostaglandin analogue
Igarashi et al. 2014 [18]		27 patients	6	Switching from prostaglandin analogue monotherapy to prostaglandin/ beta blocker fixed combination results in greater IOP reduction
Ikeda et al. 2016 [19]	Prospective interventional	30 patients	6	Latanoprost and tafloprost have equivalent efficacy and safety
Inoue et al. 2016 [20]	Case series	209 patients	NA	From 0 to 15% of NTG patients who are treated with prostaglandin analogues are classified as non-responders. The rate of non-responders were lower with bimatoprost
Inoue et al. 2012 [20]	Prospective interventional	76 patients	36	BAK-free travoprost is an effective drug to reduce IOP for at least 3 years
Kim et al. 2011 [21]	Case series	166 patients	24	Long term use of latanoprost may decrease CCT in patients with NTG
Mizoguchi et al. 2012 [22]	RCT	116 patients	3	Tafluprost and travoprost are equally effective to decrease IOP in NTG
Naito et al. 2016 [23]	Prospective interventional	30 patients	3	IOP lowering effect of travoprost persists during the day
Nakano et al. 2011 [24]	Prospective interventional	44 patients	3	Tafluprost is a safe and effective drug for NTG patients with IOP <16mmHg
Sato et al. 2011 [25]	Prospective interventional	18	3	Switching to bimatoprost in NTG patients who are not responsive to latanoprost can lead to additional IOP lowering
Shin et al. 2014 [26]	Prospective interventional	50 patients	NA	Both tafluprost and travoprost decrease the IOP and increase the ocular perfusion pressure in NTG patients. Travoprost is more effective than tafluprost to reduce IOP in evening

BAK: Benzalkonium; CCT: Central Corneal Thickness; RCT: Randomized Clinical Trial.

abstract in English.

IOP lowering medications

The first line of treatment in NTG patients is antiglaucoma medication to slow the progression of visual field and structural changes. Table 1 summarizes the results of studies investigating the role of medical therapy in NTG.

α2 agonist: It is shown that brimonidine can improve retinal blood flow circulation in patients with NTG and retinal vascular dysregulation, although there was no change in visual function of patients who were treated with this drop [9]. Furthermore, the addition of a newly formulated brimonidine drop in NTG patients who are already under treatment can result in further reduction in IOP with minimal adverse effects [10]. It is also demonstrated that brimonidine has an add-on effect in NTG patients who require further IOP reduction despite IOP <16mmHg with a prostaglandin analogue [17].

Beta blockers: In a study by Araie et al. [11] risk factors for progression of glaucoma in patients who are receiving a beta blocker have been assessed. They found that the presence of optic disc hemorrhage and less extent of myopia is associated with increased risk of glaucomatous damage in non-highly myopic NTG eyes with mild to moderate damage in whom the IOP is less than 13mmHg with a beta blocker drop.

In a multi-center randomized controlled trial, brimonidine timolol fixed combination drop was found to be safer and more effective compared to 0.5% timolol ophthalmic solution in a Korean population with NTG [12]. In an earlier study, the safety and efficacy of a dorzolamide-timolol fixed combination ophthalmic solution was proved in patients with NTG up to 3 months follow-up [13]. Dorzolamide timolol fixed combination was found to have additive IOP lowering effect in patients receiving a prostaglandin analogue [16]. Another study found that this combination has an equal efficacy with latanoprost in terms of IOP control and ocular perfusion pressure [15]. Furthermore, this drug does not drop the ocular perfusion pressure and diastolic ocular perfusion pressure, although it can decrease the diastolic blood pressure in the afternoon [31].

Prostaglandin analogues: In a case-series study, bimatoprost was found to be the most effective prostaglandin analogue in terms of IOP reduction compared to latanoprost and travoprost. 0% to 15% of NTG patients were identified as non-responders depending on the type of prostaglandin analogue used. The rate of non-responders was lower among patients who received bimatoprost [20]. Switching to bimatoprost resulted in significant reduction of IOP in a Japanese population with NTG and insufficient response to latanoprsot [25]. Latanoprost and tafluprost had an equivalent efficacy in terms of IOP control in a study by Ikeda et al., the rate of adverse effects such as eyelash changes, iris pigmentation, conjunctival injection and corneal

Table 2: Published papers on surgical management of NTG.

Type of Surgery	Author, year	Study design	No. of eyes	F/U (m)	IOP Findings
Trabx + MMC	Iverson, 2016 [35]	retrospective	15	Mean of 71 months	*35% IOP reduction (4.63mmhg) after Trabx *IOP ≤10 in 87, 80, 80, and 66% of eyes at 1,2,3, and 4 years respectively *improved slope of MD and PSD (halting the VF progression)
	Jayaram, 2016 [36]	retrospective	131	Range of 12 to 48	*25% reduction in IOP without medication in 92,77,67,64% of eyes at 1,2,3, and 4 years respectively
	Schultz, 2016 [37]	prospective	32	Mean of 50	* IOP ≤10 in 90, 79, 79, 68% of eyes at 1,2,3, and 4 years respectively
	Naito, 2017 [38]	retrospective	17	24	*41% IOP reduction (5.8mmHg) * IOP ≤10 in 70% of eyes at 2 years *92% of eyes with IOP ≤10 showed improvement in MD slope
SLT	Nitta, 2013 [39]	prospective	42	36	*IOP reduction from 15.8 to 13.2, 13.5, and 13.5 at 1,2, and 3 years respectively
	Tojo, 2013 [40]	prospective	10	3	*IOP reduction from 13.5 to 10.1, 11.2, and 11.3 at 1,2, and 3 months respectively
	Lee, 2014 [41]	Prospective cohort	60	1	*20% reduction in IOP without changing the medications in 60% of eyes
	Lee, 2014 [42]	Prospective cohort	18	1	*20% reduction in IOP without changing the medications in 44% of eyes *17% IOP reduction (2.6 mmHg) at 1 month
	Lee, 2015 [43]	Prospective cohort	83	6	*20% reduction in IOP off-medications in 61% of eyes * A higher IOP reduction was correlated with a higher baseline IOP
	Lee, 2015 [44]	Prospective cohort	41	12	*20% reduction in IOP without medication in 22% of eyes
	Lee, 2015 [45]	Prospective cohort	34	24	*20% reduction in IOP without medication in 11% of eyes
Sclerectomy ± MMC	Suominen, 2014 [46]	Prospective, randomized	37	12	*25% reduction in IOP without medication in 50% of eyes *IOP ≤10 with or without medication in 17 eyes *lower post-op IOP in MMC group without increased complications
	Lei, 2015 [47]	Prospective, randomized	60	12	Higher average visual acuity and functional filtering bleb formation with lower post-op recurrence rate in MMC group
	Harju, 2017 [48]	Prospective, randomized	37	Median of 94 months	*25% reduction in IOP without medication in 50% eyes *No difference in long-term IOP between two groups
VC/PVC	Ho, 2017 [49]	Retrospective	94	36	*24.5% IOP reduction *12% complications

IOP: Intraocular Pressure; MD: Mean Defect; MMC: Mitomycin C; PSD: Pattern Standard Deviation; SLT: Selective Laser Trabeculoplasty; Trabx: Trabeculecotmy; VC/PVC: Viscocanalostomy/Phacoviscocanalostomy; VF: Visual Field.

epitheliopathy was not significantly different between the two drugs [19].

Benzalkonium (BAK)–free travoprost was found to be effective in reducing IOP for at least 3 years; however the visual field changes tended to progress in 2.8%-13.9% of NTG patients [20]. The IOP lowering effect of travoprost persists during the day at a clinically significant level [23], this effect of travoprost last for up to 72 hours after the instillation of the last dose [32]. However, it does not improve the ocular perfusion pressure [32]. Bimatoprost [33] and tafluprost [34] are also effective to reduce IOP in NTG. In a study by Nakano et al. [24] topical administration of tafluprost induced significant IOP reduction in untreated NTG patients with a baseline IOP ≤16mmHg. Another study demonstrated that once-daily administration of tafluprost or travoprost has an equivalent IOP lowering effect [22].

In a retrospective study of 128 patients with NTG, long-term use of latanoprost was found to decrease central corneal thickness (CCT). This finding has large implications in the follow-up of NTG patients for proper IOP targeting and management [21]. In a RCT by Shoji et al. authors reported that tafluprost timolol fixed combination ophthalmic solution is more effective in decreasing IOP compared to latanoprost timolol fixed combination in a group of patients with NTG after 3 months [27].

Surgical treatment

Although most patients achieve therapeutic IOP target with medications, some fail to respond. This would be challenging especially in progressive functional or anatomical damage while there is no elevated IOP [35]. Surgical intervention is the next option in these refractory cases. Results of studies evaluating the outcome of surgery in NTG patients are summarized in Table 2.

Trabeculectomy: It was shown that an IOP of ≤10 or an IOP reduction of at least 20% is associated with the stability of VF in NTG patients after trabeculectomy (Trabx) [50]. Four studies evaluated Trabx+MMC efficacy in NTG patients with measuring the percentage of eyes with single digit IOP or effective IOP reduction during follow-up (Table 2). Naita et al. reported that 70% of eyes experienced post-op complications [38]. The most common was transient hypotony (50%), and three eyes experienced significant VA decline probably due to the hypotony maculopathy. Although the mean post-op IOP was not statistically different between eyes with declined VA and normal VA, the authors recommended careful follow-up in IOP<7 due to an increased probability of VA decline [38]. Two similar studies evaluated the safety of the Trabx and reported the hypotony in 50% of eyes as the most common complication but without any significant visual loss [35,37]. Jayarem et al. conducted a trial with Moorfields Safer Surgery technique with controlled posterior aqueous flow and formation of diffuse drainage blebs [36]. They reported a significantly lower early and late complications.

Selective laser trabeculoplasty (SLT): This method not only provides the surgeon with favorable IOP reduction but also decreases the IOP fluctuations, which is considered as a risk factor for progression in NTG [51]. Tojo et al. evaluated the effect of SLT on IOP fluctuations. They found that SLT decreases nocturnal IOP fluctuations but it has no effect on diurnal IOP fluctuations [40]. Another study reported higher pre-SLT IOP and greater IOP reduction at one-week post-SLT as the predictors of successful outcome after one month [41]. In a series of prospective cohort studies, Lee et al. studied the patients who had undergone SLT [43-

Table 3: Published papers on neuroprotective agents studied on human.

Agent	Author, Year	Design	Findings
Ginkgo	Cybulska, 2012 [53]	Review	Anti-oxidative capacity, improving ocular microcirculation, some reversibility in VF progression
Ginkgo – Anthocyanin	Shim, 2012 [54]	Retrospective; (GBE n=103, Anth n=132, Control n=97)	Improvement in both VF and BCVA
Ginkgo	Lee, 2013 [55]	Retrospective (n=42)	Slowing the progression of VF damage
Ginkgo	Guo, 2013 [56]	RCT (n=35)	No effect on VF and contrast sensitivity
Palmitoylethanolamide	Costagliola, 2014 [57]	RCT (n=32)	IOP reduction and improvement in VF

BCVA: Best Corrected Visual Acuity; IOP: Intraocular Pressure; RCT: Randomized Clinical Trial; VF: Visual Field.

45]. The rate of acceptable IOP reduction was 61, 22 and 11% at 6, 24, and 48 months [43-45]. The SLT procedure was associated with minor complications such as conjunctival hyperemia, eye discomfort, and pain. No major complication was reported [39].

Non-penetrating glaucoma surgery (NPGS)

Viscocanalostomy: Viscocanalostomy is a non-penetrating technique introduced in 1990 for treatment of glaucoma and is associated with fewer complications compared to trabeculectomy or sclerotomy [52]. There is no hypotony or over-filtration as there is no entry into the AC. It can also be combined with phacoemulsification cataract surgery (PVC) [49]. Ho et al., in a retrospective study reported that IOP reduction after one year was about 25% and it persisted for at least three years. However, the percentage of eyes receiving antiglaucoma drops raised from 5% to 25% during three years. Few complications such as cystic blebs, cystoid macular edema, and hyphema were reported [49].

Deep Sclerectomy (DS): Three trials were conducted, and the efficacy of DS with and without the MMC was evaluated (Table 2). All three studies stated the significant IOP reduction after this procedure with a low rate of complications [46-48]. Suominen et al. reported significant IOP reduction in MMC group with total success (IOP reduction>25%) of 67% compared with the non-MMC group with total success of 41% at one year [46]. However, in a long-term follow-up trial, Hajru et al. reported a significant decrease of IOP after DS, but they didn't find any difference in IOP reduction between MMC and non-MMC groups [48]. In 8 years' follow-up period no cases of shallow AC, hypotony maculopathy, hyphema, bleb leakage, and infection occurred [48].

Neuroprotective agents

NTG is a type of chronic primary open angle glaucoma (POAG) with normal IOP. The difference is lying in pathophysiology and etiologic triggers. Two underlying mechanisms are suggested that might damage the optic nerve head in NTG; a stretching of the lamina cribrosa and RGC damage due to the elevated IOP, and reduced blood flow to the optic nerve head [58]. It seems that vascular factors are more important in the pathophysiology of NTG. Low blood pressure, nocturnal hypotension, orthostatic hypotension, sleep apnea, Raynaud's phenomenon, and migraine, all are possible risk factors for ischemic stress in the pathophysiology of NTG [59,60]. Astrocytes are the most important glial cells in the optic nerve head. Ischemic insult leads to the astroglial activation, which alters the microenvironment by upregulating cellular products and mediators [57]. NO is one of these mediators which is a free radical with high diffusibility and is upregulated by astroglial activation. NO is not damaging to the tissue due to its very short half-life, but when it spreads into the adjacent axons with a high concentration of superoxide radicals, the resultant peroxynitrite (ONOO-) will be ultimately damaging [61]. The other major event in altering microenvironment is triggering the efflux of glutamate from glial cells and influx of calcium into the neural cells with subsequent formation of free radicals [62]. Moreover, ischemia causes oxidative stress which leads to the breakdown of DNA molecules in neurons, upregulation of endothelin 1 (which in turn activates astroglial cells), heat shock proteins (HSP), and matrix metalloproteinase 2 (MMP-2) and MMP-9 [62,63]. Extensive research is currently underway to produce drugs that stop optic nerve head damage by altering the above-mentioned mechanism. Table 3 summarizes the results of recent studies evaluating the outcome of these "neuroprotective drugs" on human subjects.

Ginkgo: The use of Ginkgo Biloba Extraction (GBE) for medical purposes has an ancient history especially in the treatment of vascular disorders such as cerebrovascular insufficiency, cognitive impairment, tinnitus and hypoxia, and in preventing the aging process [55]. In 1991, Raabe et al. documented its efficacy on visual field distortion in chronic CNS ischemia in elderly patients [64]. In 2003, Quaranta et al. conducted an RCT to evaluate the efficacy of GBE in NTG patients [65]. In the recent decade, different studies evaluated the efficacy of GBE administration to halt the progression of glaucoma. In our literature search, four pertinent studies were found; one review, two retrospective studies and one randomized clinical trial (Table 3).

Cybulska et al. in a review article discussed the pharmacological properties of GBE as an antioxidant, anti-inflammatory, anti-thrombosis, and anti-vasospastic agent [53]. Mitochondrial dysfunction plays a crucial role in glaucomatous optic neuropathy, and it is proven that GBE stabilizes the mitochondrial function and prevents the formation of free radicals [53]. As an anti-thrombosis agent, authors documented that GBE improves retinal microcirculation and reduces the ischemic insult in diabetic rat retina [66]. Diffusion of microenvironment mediators such as endothelin and MMP surrounding the optic nerve head may lead to disturbance of microcirculation and vasoconstriction. Fluctuations in microcirculation weaken the blood-brain barrier and manifest itself as splinter hemorrhage [53]. GBE has a beneficial effect in the treatment of subarachnoidal hemorrhage as an anti-vasospastic agent [67]. Hence, its positive effect would be probable in the same manner in the optic nerve head. They also discussed the safety issues in GBE administration and concluded that there would be no significant concern about the long-term use of GBE comparing with the placebo. Although some cases of bleeding are reported, the direct relationship is not established [53].

In 2012, Shim et al. compared VF mean deviation and BCVA in 103 NTG patients who were treated with GBE and 97 controls in follow-up period of 23.82 ± 9.84 months, and reported improvement in VF; MD change from -5.25 (±6.13) to -4.31 (±5.60) (p=0.002), but the final BCVA was not different between two groups [54]. The study was retrospective and follow-up time was limited to 2 years after treatment. One year later Lee et al. evaluated the long-term effect of GBE in 42 patients in a retrospective study [55]. They compared the VF progression in the same patient before and after the treatment with GBE and followed the patients for four years. They reported that the regression coefficient of MD, PSD, and Visual field index (VFI) improved significantly after treatment with GBE (P<0.001), especially in the superior central field. However, it was a retrospective study with small sample size. In the same year, Guo et al. conducted a randomized cross-over clinical trial on 28 patients for eight months and reported no improvement in MD or contrast sensitivity in contrary to previous reports [56].

Palmitoylethanolamide: Astroglial activation is accompanied by microenvironment molecular cascades such as glutamate efflux [62]. In the eye, there are protective mechanisms to counteract glutamate efflux such as activation of peroxisome proliferator-activated receptor (PPAR) [68]. Palmitoylethanolamide (PEA) is a natural amide of ethanolamide and palmitic acid with relatively high affinity to PPAR [57]. Costagliola et al. assessed the effect of oral administration of PEA in VF progression in NTG patients [57]. They studied 32 patients in a randomized clinical trial over six months' period and reported IOP reduction of 17% (2.2mmHg) in treatment group vs. control group. They also reported significant improvement in VF parameters; MD of -7.65+-6.55 dB vs. -4.55+-5.31, and PSD of 5.21+-4.08 vs. 3.81+-3.02 with p-values <0.001 and <0.02 respectively.

New targets in experimental studies: The glutamate transporters are the only mechanism for clearance of extracellular glutamate [69]. There are three main glutamate transporters in the inner plexiform layer across retinal ganglion cells (RGCs); glutamate transporter 1 (GLT-1) in the bipolar cells, excitatory amino acid carrier 1 (EAAC1) in the RGCs, and glutamate/aspartate transporter (GLAST) in the Muller cells [70,71]. It is shown that suppressing the expression of GLAST and EAAC1 in mice would lead to progressive RGC loss without elevated IOP, similar to the events in NTG neuropathy [72]. To assess the efficacy of targeting these pathways, anatomical and functional evaluation should be included. Candesartan, Spermidine, and Edaravone suppress nitric oxide synthase (NOS) and scavenger free radicals [73-75], while Apolipoprotein E-containing lipoproteins (Apo E-LP) and Valproic acid are effective mediators in the modulation of glutamate neurotransmission [76,77]. Geranylgeranyl acetone (a heat shock protein) can also prevent RGC loss [63].

Conclusion

NTG is a type of glaucomatous optic neuropathy with similar features to POAG. However, the exact pathophysiology and mechanism of this entity remains to be elucidated. Although IOP by definition, is normal in these patients, IOP modification is still the best established target for treatment. The first line of treatment is usually anti-glaucoma ophthalmic solutions. If despite maximum medical therapy the disease progression would not stop, surgical options should be offered to the patient. The role of neuroprotection is emerging in the treatment of NTG. Neuroprotective agents can theoretically improve the function of RGCs and optic nerve and thus they are an interesting area of investigation.

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