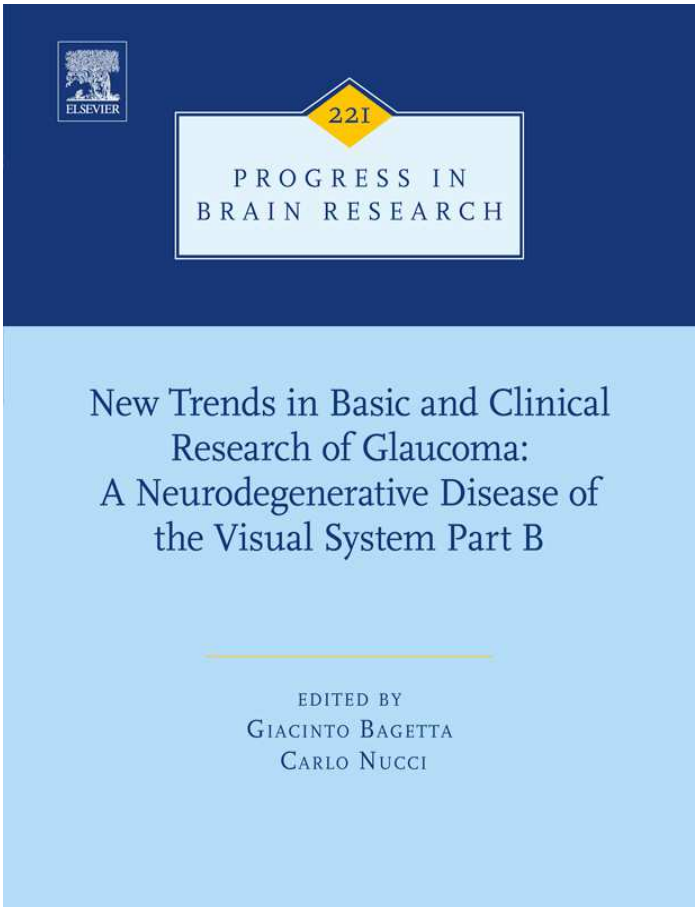

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CHAPTER

Advance in the pathogenesis and treatment of normal-tension glaucoma

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Rodolfo Mastropasqua*[,1], Vincenzo Fasanella[†,1], Luca Agnifili[†], Michela Fresina[‡], Silvio Di Staso[§], Angela Di Gregorio[§], Giorgio Marchini*, Marco Ciancaglini[§,2]

**Ophthalmology Unit Department of Neurological, Neuropsychological, Morphological and Movement Sciences, University of Verona, Verona, Italy*

[†]Department of Medicine and Aging Science, Ophthalmology Clinic, University G. d'Annunzio of Chieti-Pescara, Chieti, Italy

[‡]Department of Specialist, Diagnostics and Experimental Medicine (DIMES), Ophthalmology Service, University of Bologna, Bologna, Italy

[§]Ophthalmic Clinic Department of Surgical Science, Eye Clinic, University of L'Aquila, L'Aquila, Italy

[2]Corresponding author: Tel.: +39-0862-368634; Fax: +39-0862-368555, e-mail address: marco.ciancaglini@cc.univaq.it

Abstract

Normal-tension glaucoma (NTG) is a multifactorial disease where mechanical stresses and vascular alterations to the optic nerve head probably represent the key pathogenic moments. Although intraocular pressure (IOP) plays a crucial role in the retinal ganglion cell loss, the IOP reduction does not necessarily reduces the disease progression. Therefore, several IOP-independent factors such as glutamate toxicity, oxidative stress, autoimmunity, and vascular dysregulation have been considered in the pathogenesis of NTG. Numerous evidences documented an impairment of the ocular blood flow, involved both in the onset and progression of the disease. The IOP reduction remains the main strategy to reduce the damage progression in NTG. Recently, new treatment strategies have been proposed to improve the control of the disease. Neuroprotection is a rapidly expanding area of research, which represents a promising tool. In the present review, we summarize the recent scientific advancements in the pathogenesis and treatment of NTG.

Keywords

NTG, NTG pathogenesis, NTG therapy, Neuroprotection, Vascular dysregulation

[1]R. M. and V. F. equally contributed to this work and share primary authorship.

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1 INTRODUCTION

Normal-tension glaucoma (NTG) is a multifactorial disease, with several risk factors concurring in the final optic nerve damage.

First, demographic factors may play a significant role. The prevalence of NGT varies with race and age since is higher in Asian, such as Japanese or Chinese, than in white or African populations. (Cho and Kee, 2014), and the mean age of patients with NTG is in the 60s. Second, vascular risk factors play a crucial role in the pathogenesis of NTG. These include vasospasm, vascular and systemic diseases, and migraines. In many studies, it was found that ischemic stroke, due to small or large-artery atherosclerosis, was a significant risk factor for having glaucomatous cupping of the optic disk with normal intraocular pressure (IOP) (Doyle et al., 2005; Drance et al., 2001; Gungor et al., 2011; Hayreh, 1999; Phelps and Corbett, 1985; Schulzer et al., 1990; Tian and Liu, 2011). Furthermore, high blood pressure and impaired glucose tolerance were associated with an increased prevalence of NTG (Kim et al., 2014; Newman-Casey et al., 2011), though these findings were not uniquely recognized (Leske et al., 2002; Quigley et al., 2001; Tielsch et al., 1995). Third, also IOP significantly contributes to the pathogenesis of the disease, though literature evidences are opposite. The Low-Pressure Glaucoma Treatment Study (Greenfield et al., 2007) showed that eyes with higher IOP did not present worse perimetric damage, this suggesting a limited influence of the IOP. Conversely, in studies of asymmetric NTG (Cartwright and Anderson, 1988; Crichton et al., 1989; Haefliger and Hitchings, 1990) the eye with a higher IOP showed greater glaucomatous damage, this sustaining a pressure-sensitive component. Accordingly, the Collaborative Normal-Tension Glaucoma Study Group (CNTGS) (1998a) reported a positive effect of the IOP lowering in reducing the risk of progression.

The treatment of NTG still represents an unsolved problem for the ophthalmologists, since the only validated therapy to control the optic nerve damage consists in lowering the IOP, even though the real importance of this risk factor in the onset and progression of this disease has not been definitely clarified. The most significant recent advances in the pathogenesis and treatment of NTG will be discussed in the present review.

2 ADVANCE IN THE PATHOGENESIS OF NORMAL-TENSION GLAUCOMA

2.1 VASCULAR AND MECHANICAL FACTORS

The vascular and mechanical theories are the main theories considered in the pathogenesis of the glaucomatous optic neuropathy in patients with NTG.

In the vascular theory, the main role seems to be played by the ocular blood flow (OBF) impairment. The reduction of OBF leads to the retinal ganglion cells (RGC) loss by inducing a chronic ischemia or damage subsequent to reperfusion injury (Flammer et al., 2002).

There are several factors potentially reducing the OBF. The vascular dysregulation is one of the main mechanisms invoked. It is defined as the inability of a tissue to maintain a constant blood supply despite changes in perfusion pressure secondary to vascular abnormalities or to the role of local vasospastic/vasodilating agents (Fig. 1).

Also the blood pressure has a predominant role: several studies reported that low blood pressure was a significant risk factor for visual field defect progression in NTG (Leighton and Phillips, 1972; Okumura et al., 2012). However, the real association between these findings is still debated.

In a recent study in patients with NTG, Abegao Pinto et al. (2012) reported the reduction of blood flow velocities in retrobulbar arteries and in cerebral circulation. They found that, while in healthy individuals there was a linear correlation between vascular pulsatility index and resistive index, this relation was not present in NGT patients. Su et al. (2006, 2008), using the brachial artery ultrasound assessment of endothelium-dependent flow-mediated vasodilation, provided evidence of a generalized endothelial dysfunction in patients with NTG.

The vascular dysregulation in NTG was also related to alterations of local agents. Henry et al. (1999, 2006) documented an altered vascular reactivity to endothelial vascular dysregulation factors. This should be intended as expression of an impairment of the peripheral endothelium-mediated vasodilatation, Buckley et al. (2002) analyzed cutaneous artery biopsies showing a selective defect in the agonist-mediated release of endothelium-derived vasodilators. These findings support the

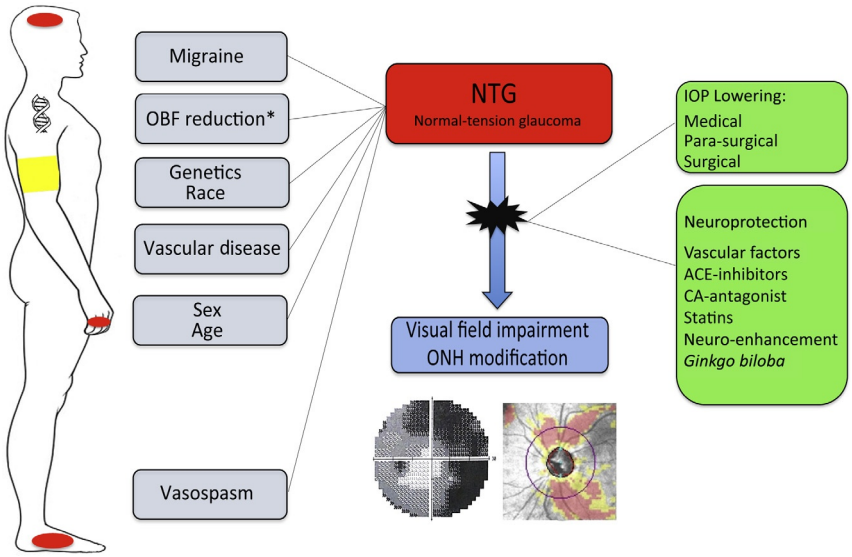

FIGURE 1

Schematic representation of the risk factors, pathogenesis, and the current therapy of NTG. *OBF, ocular blood flow.

concept of a generalized vascular endothelial dysfunction in patients with NTG. In a recent study, modifications of plasmatic levels of endothelin 1 (ET-1) and nitric oxide (NO) (Galassi et al., 2011) were documented. However, it is not clear whether these changes promote the optic nerve damage or occur after the damage initiation. In studies on vascular dysregulation, numerous authors focused on the diameter of retinal vessels (Drance et al., 1988; Mitchell et al., 2005; Rader et al., 1994; Rankin and Drance, 1996). Chang et al. (2011) found that the mean central retinal vessel diameters were smaller in patients with NTG than in normal subjects. However, it remains unclear whether this finding was a cause or a result of the optic neuropathy. In addition, the authors found an association between vessel diameter (evaluated as central retinal arteriolar equivalent), RNFL thickness, and IOP.

The mechanical theories of the glaucomatous optic neuropathy in NTG consider both the IOP and trans-lamina cribrosa pressure.

Increased levels IOP induce a mechanical stress that finally leads to elongation, stretching, bowing, and collapse of the lamina cribrosa beams. Therefore, the axons of the RGC are damaged directly, by the increased pressure gradient, or indirectly, by the tissue deformation (Flammer et al., 2002).

The assessment of the aqueous humor (AH) hydrodynamics, especially the trans-scleral outflow pathway, has recently provided additional support on the potential role of the IOP in the pathogenesis of NTG. In the last years, our research group conducted a series of studies focused on the evaluation of the trans-scleral AH outflow by using the laser scanning *in vivo* confocal microscopy (Carpineto et al., 2011; Ciancaglini et al., 2008a,b, 2009; Mastropasqua et al., 2013, 2014a,b). This methodology can indirectly evaluate the trans-scleral AH percolation by noninvasively assessing the conjunctiva, which is the terminal part of the trans-scleral pathway.

The signs of the trans-scleral AH outflow are represented by the presence of conjunctival epithelial microcysts, which are hypo-reflective cystic spaces intended as bubbles of percolating AH.

Interestingly, Agnifili et al. (2012) reported these microcysts also in patients with NTG. The presence of microcysts supports the hypothesis of a change in AH hydrodynamics and the activation of alternative outflow pathways, such as trans-scleral routes, also in NTG.

Currently, the possibility to assess the nictemeral behavior of IOP by using a contact lens sensor better clarified the role of IOP fluctuations in the pathogenesis of NTG.

In a different study, Agnifili et al. (2015) documented the presence of nocturnal acrophase and prolonged IOP peaks in 80% of patients with medically controlled NTG, even though these phenomena were less pronounced with respect to POAG. Moreover, patients with NTG showed a 96% greater variation of IOP (measured in mV equiv.) compared with healthy subjects.

The other mechanical theory considers the role of the trans-lamina cribrosa pressure in the RGC damage. Since in NGT the IOP falls within the normal range, it was hypothesized that the mechanical damage could be linked to an imbalance of the trans-lamina cribrosa pressure, which is the difference between IOP and orbital

cerebrospinal fluid pressure (Morgan et al., 2008). This pressure difference could result in a baro-traumatically induced optic nerve damage (Wostyn et al., 2013) promoted by a modification of the intracranial pressure, which tends to decrease. In agreement with this theory, recent studies reported lower intracranial pressure in patients with NGT with respect to POAG or healthy subjects (Berdahl et al., 2008; Ren et al., 2010). Jaggi et al. (2012) found an increase of optic nerve sheath diameter in patients with NGT, which is a feature normally related to an increased intracranial pressure. They suggested that a higher intracranial pressure could lead to an expansion of the meningeal sheath around the optic nerve, with consequent axonal compression and reduction of the blood flow.

Recently, the obstructive sleep apnoea–hypopnea syndrome (OSAHS) was hypothesized to play a role in the NTG-related optic neuropathy (Perez-Rico et al., 2014). In support of this, OSAHS is becoming widely accepted as a risk factor for different forms of open-angle glaucoma, including NTG. Patients with OSAHS, without anamnestic history of glaucoma, may present increased IOP values (possibly related to increased body mass index), thinning of retinal nerve fiber layer alteration of visual field indices (Hashim et al., 2014; Perez-Rico et al., 2014; Stein et al., 2011), suspicious glaucomatous disk changes, and anomalies in electrophysiological tests (Gutierrez-Diaz et al., 2012).

In patients with OSAHS, the optic nerve damage was related to vascular and mechanical factors (Perez-Rico et al., 2014). Vascular factors included recurrent hypoxia with increased vascular resistance, autonomic deregulation, oxidative stress, inflammation (linked to the hypoxia and the subsequent reperfusion), and decreased cerebral perfusion pressure. Mechanical factors included an increased nocturnal IOP, related to the supine position and obesity, an increased intracranial pressure, and elastic fiber depletion in the lamina cribrosa and/or trabecular meshwork (TM).

2.2 OXIDATIVE STRESS, NEUROTOXICITY, AND AUTOIMMUNITY

Although the IOP and its fluctuations may play a crucial role, various IOP-independent factors (glutamate toxicity, neurodegenerative processes, oxidative stress, hormones, and autoimmunity) are also involved in the development of glaucomatous optic neuropathy in patients with NTG (Harada et al., 2007; Namekata et al., 2009). The oxidative stress is one of the most important IOP-independent factors considered in the optic nerve damage in these patients (Bunting et al., 2010; Harada et al., 2007; Namekata et al., 2009).

Several studies focused on the potential role of glutamate and glutathione (GSH) in inducing the optic nerve damage (Gherghel et al., 2013; Yuki et al., 2010). The glutamate uptake by glial cells is an important mechanism for promoting efficient interneuronal signaling in the central nervous system. In addition, the glutamate is also a neuroprotective agent.

GSH is an antioxidant factor playing an important role in defending cells against the oxidative stress. The glutamate/aspartate transporter (GLAST), which represents the major glutamate transporter, maintains the extracellular levels of glutamate

below the neurotoxic threshold and preserves the physiological concentration of GSH by transporting glutamate (a substrate for GSH synthesis) into glial cells. Studies on animal models of NTG reporting a correlation between oxidative stress-induced RGC damage and glutamate are progressively increasing (Harada et al., 2007; Namekata et al., 2009). Harada et al. (2010) found that some polymorphisms leading to the loss of GLAST can induce RGC apoptosis in transgenic mice, even though there is still no *in vivo* evidence of elevated glutamate plasma levels in NTG (Bunting et al., 2010). Gherghel et al. (2013) documented that NTG patients exhibit lower levels of GSH and GSH transporter (tGSH) compared to age-matched controls. The authors hypothesized a reduction of vascular NO into peroxynitrite anion (ONOO–), a highly toxic reactive nitrogen species responsible for endothelial dysfunction, as the cause of such modification.

Other antioxidant factors that have been investigated include vitamins and uric acid; particularly, lower plasmatic levels of vitamin C and increased concentrations of uric acid (Yuki et al., 2010) were described in patients with NTG. Vitamin C is a well-known dietary antioxidant vitamin, which plays a role in reducing the reactive oxygen species in the anterior chamber and within the TM. Vitamin C may reduce the IOP by promoting depolymerization of the hyaluronic acid in the TM (Linner, 1969). Also the uric acid levels in the AH may have important implications in glaucoma, since it is involved in the TM physiology, and represent a risk factor for trabeculectomy failure (Jampel et al., 1998).

Some hormones have been drawn into play in the development of NTG. In transgenic mice, aldosterone was shown to be a critical mediator of RGC damage, independently from IOP. In fact, the chronic administration of aldosterone led to RGC loss, which was prevented by the use of mineral corticoid receptor blocker (Nitta et al., 2013).

Autoimmune processes have gained a progressively increasing consideration in the pathogenesis of NTG. Increased levels of antiphosphatidylserine antibodies were documented in the serum of patients with NTG (Kremmer et al., 2001). These antibodies bind to phosphatidylserine molecules, which are shifted from the inner to the outer leaflet of the cell membranes during the early phase of apoptosis. Despite scientific evidences are unclear, also increased levels of antirhodopsin antibodies were sometimes described in patients with NTG (Romano et al., 1995; Skonieczna et al., 2014).

Autoimmunity has been also summoned for a hypothetical role of the *Helicobacter pylori* in the pathogenesis of NTG. Even though the exact pathophysiology is still unclear, this bacterium may be either a primary or a secondary factor in the development and/or progression of NTG. The most suitable hypothesis is that antibodies produced against antigens of *H. pylori* may cross-react with RGC inducing their loss (Kim et al., 2011).

2.3 GENETIC FACTORS

POAG and NTG appear to be a continuum of a heterogeneous disease, which is probably caused by the interaction of multiple genes and environmental factors (Allingham et al., 2009). Because of the presence of a normal IOP, other factors, such

as genetic predisposition, could have an important role in the pathogenesis of NTG. Furthermore, since up to 21% of NTG patients were reported to have a family history, it was suggested that these patients might be genetically predisposed (Goldberg et al., 1981). Several genes were reported to be associated with NTG.

Three causative genes were identified, even though none of them have been confirmed. The most important are optineurin (*OPTN*) (Rezaie et al., 2002), myocilin (*MYOC*) (Baird et al., 2005; Fingert et al., 1999), and WD repeat-containing protein 36 (*WDR36*) (Blanco-Marchite et al., 2011; Pasutto et al., 2008). However, evidences of their involvement are still conflicting and unclear.

Rezaie et al. (2002) found that sequence alterations in *OPTN* were present in 16.6% of 54 families with open-angle glaucoma, including those with NTG. *OPTN* is expressed in TM that not only plays a significant role in the IOP control but also acts as a potential neuroprotective agent. More recent studies hypothesized an association between the *OPTN*, NTG, and the Alzheimer's disease (Allingham et al., 2009; Liu and Tian, 2011). Other studies reported that the *OPTN* and *WDR36* variants did not predispose individuals to POAG or NTG (Wiggs et al., 2003).

An association between NTG and gene polymorphism of the endothelial type A receptor was described. ET-1, a potent vasoconstrictor, may be involved in the regulation of IOP and ocular vessel tone (Ishikawa et al., 2005; Kim et al., 2006). Optic atrophy type 1 gene (*OPA1*) was reported to be associated with NTG in the hereditary POAG family (Aung et al., 2002; Mabuchi et al., 2007). It was hypothesized that the mitochondrial *OPA1* preserves RGC from pressure-mediated retinal damage (Dai et al., 2011); moreover, altered gene expression could directly induce apoptotic cell death in cultured RGC (Ju et al., 2009; Mi et al., 2014). A more recent study confirmed the association between two polymorphisms within the *OPA1* gene and NTG but not in high-tension glaucoma (Guo et al., 2012).

An increasing number of alterations of other candidate genes were reported in NTG: mitofusin1 (*MNF1*)^{S}, mitofusin 2 (*MNF2*)^{S}, presenilin-associated rhomboid-like (Wolf et al., 2009), Toll-like receptor 4 (*TLR4*) (Shibuya et al., 2008), glaucoma 1B (*GLC1B*) (Stoilova et al., 1996), glaucoma 1F (*GLC1F*) (Murakami et al., 2010; Wirtz et al., 1999; Writing Committee for the Normal Tension Glaucoma Genetic Study Group of Japan Glaucoma Society et al., 2010), S1 RNA-binding domain (*SRBD1*), and *EVLOV5* (Writing Committee for the Normal Tension Glaucoma Genetic Study Group of Japan Glaucoma Society et al., 2010). Several studies pointed out a possible involvement of autoimmune mechanisms in the pathogenesis of glaucoma, especially in NTG. Because some glaucoma patients had increased titers of serum antibodies against retinal or optic nerve proteins, the RGC degeneration may be also promoted by an imbalance of immune regulation between proapoptotic and protective pathways (Tezel et al., 1998; Wax et al., 1998). *TLR4* is a trans-membrane receptor that mediates immune responses to exogenous and endogenous ligands. Previous studies demonstrated the implication of *TLR4* gene in NTG in the Japanese (Shibuya et al., 2008) but not in the South Korean population (Suh et al., 2011). A recent study confirmed the association of *TLR4* gene polymorphisms with POAG, NTG, and exfoliation glaucoma in a Japanese population.

Human leukocyte antigen (*HLA*) genes regulate the immune system and the predisposition to several autoimmune disorders. *HLA* class II alleles were shown to be associated also with glaucoma (Gil-Carrasco et al., 1994, 1999). Suzuki et al. (2010) did not find any association between *HLA-DRB1* and *HLA-DQB1* polymorphisms and the risk of NTG development in Japanese subjects.

Changes in blood lymphocytes gene expression were observed in previous glaucoma studies (Golubnitschaja et al., 2004; Golubnitschaja-Labudova et al., 2000). Flammer et al. (2002) found an upregulation of *RAR* gene (RAR-related orphan receptor C) in blood lymphocytes of Caucasian patients with NTG, which could be involved in modulation of immune response and apoptosis (Fraenkl et al., 2013).

In other studies, it was reported and confirmed the association of a duplication of thank-binding kinase 1 (*TBK1*) gene on chromosome 12p14 and NTG (Fingert et al., 2011; Kawase et al., 2012; Ritch et al., 2014). *TBK1* was expressed in the ganglion cells and in the microvascular structures of the human retina and seems to have a role in the apoptotic or vascular damage in patients with glaucoma. The chromosome 12q14 duplication may lead to NTG via dysregulation of *TBK1* expression.

Chronic oxidative stress was implicated as a possible cause of TM cell loss even though the exact molecular mechanism underlying this phenomenon is still unclear. Chronic oxidative stress leads to the endogenous production of reactive oxygen species by mitochondria in TM cells, thereby increasing the level of oxidative damage in the tissue (Li et al., 2007). In glaucomatous patients, a spectrum of mitochondrial abnormalities involving oxidative stress and implying mitochondrial dysfunction or altered mitochondrial pathways was found (Abu-Amero et al., 2006; Izzotti et al., 2011; Osborne, 2008). Jeoung et al. (2014) recently identified a mitochondrial DNA variant in Korean NTG patients, which may be a genetic risk factor for the development of this disease.

To date, for some genes, there is evidence in tissue culture and animal models of their functions; but for many genes, large demographic data to support their classification as major risk factors for developing NTG are still lacking. Further investigations are needed to identify new more genes and to clarify their role.

3 ADVANCE IN THE TREATMENT OF NORMAL-TENSION GLAUCOMA

In untreated NTG, IOP is always in the statistically normal range, usually 21 mm Hg. IOP is recognized as the most important risk factor for the development and progression of the optic neuropathy also in patients with NTG and is the only modifiable factor to control the disease (CNTGS, 1998a,b). In fact, though NTG is a multifactorial disease, the current management of this glaucoma sub type continues to focus on lowering IOP (Collaborative Normal-Tension Glaucoma Study Group, 1998b; Heijl et al., 2002). The IOP reduction, however, does not necessarily slow or shut down disease progression. It is usually easy to reduce high pressure, but it is much more difficult to achieve a considerable reduction of IOP when it falls in the normal range.

3.1 IOP-LOWERING THERAPY

3.1.1 Medical Therapy

The Collaborative Normal-Tension Glaucoma Study Group (CNTGS) (1998a,b) established that lowering IOP by at least 30% favorably altered the course of progression of visual field defects in patients who were found to have glaucomatous optic nerve damage. It was noted that the rate of progression of the untreated patients was highly variable. Approximately, 50% of untreated patients showed a localized visual field progression after 7 years, and the change was usually small and slow. The main risk factors related to progression of the untreated disease were identified as female gender, migraine, and the presence of a disk hemorrhage at baseline (Anderson et al., 2001). The authors suggested that different factors might contribute to the glaucomatous optic neuropathy with IOP-independent risk factors potentially interacting with the IOP. This interaction may affect the final benefit of the IOP lowering.

In the CNTG, the main outcome was to reduce the IOP at least of 30% with respect to baseline by using medical, laser, and surgical therapy. The outcome was reached in about half of the patients using only the medical therapy.

In a multi-center, prospective comparative study examining the effects of 0.25% nipradilol, and 0.5% timolol on visual field in Japanese patients with NTG, it was found that IOP-related factors were not significant prognostic factors (Makoto et al., 2012). Moreover, the impact of the disk hemorrhage or the extent of myopia in the NTG progression was significantly higher compared to the IOP values. In a recent 12-month follow-up study, the authors (Martha et al., 2013) reported that the amount of IOP reduction was related to the NTG progression, with lower percentage reduction being a consistent risk factor for progression. They reported that disk hemorrhage was another important risk factor for NTG progression, confirming the presence of non-IOP-dependent mechanism in the pathogenesis of NTG. These findings represent proofs of the existence of two parallel mechanism of damage in the NTG-related optic neuropathy.

Besides the IOP-lowering capability, other factors should be considered when selecting medications, such as adverse effects, ease of administration, and indications to ensure the appropriate therapeutic strategy for each individual patient. In NTG, some class of medications such as beta-blockers, carbonic anhydrase inhibitors, and alpha-agonist could sometimes have a negative effect due to alterations of retinal and optic nerve head blood circulation. However, when a single drug is unable to sufficiently reduce IOP, these classes of medications can be considered.

A few studies evaluated the efficacy of carbonic anhydrase inhibition and alpha adrenergic agonists in patients with NTG. Some evidences documented that dorzolamide increases retinal blood flow velocity in patients with NTG (Sugrue, 2000). However, literature are contrasting: in fact, in a 1-month follow-up study, dorzolamide lowered IOP by 17% but did not produce significant improvement in retrobulbar hemodynamic, as viewed with color-Doppler ultrasonography (Harris et al., 2000).

Brimonidine tartrate 0.2% (an alpha2-adrenergic agonist) was specifically studied in patients with NTG in the Low-Pressure Glaucoma Treatment Study

(Krupin et al., 2011). In this study, the authors reported that patients treated with brimonidine 0.2% were less likely to have visual field progression than patients treated with timolol 0.5%. Given that a similar IOP reduction was found between patients receiving timolol maleate 0.5% and patients receiving brimonidine, the authors hypothesized that the lower rate of visual field progression in brimonidine-treated patients could result from an IOP-independent process such as the RGC neuroprotection.

In line with this theory, previous studies demonstrated that alpha2-adrenergic agonists exert a neuroprotective activity on RGC in experimentally induced optic nerve injury, in animal models of glaucoma, in ischemia-induced optic nerve damage, and in photoreceptor degeneration (Saylor et al., 2009). Moreover, brimonidine may modulate the retinal vascular tone altering the NO signaling (Rosa et al., 2006) and may promote a correct functioning of the retinal vascular autoregulation in NTG patients (Feke et al., 2014). Thus, the use of brimonidine in the treatment of NTG should be considered.

Prostaglandin analogs (PGAs) have become the first-line treatment in patients with glaucoma. This clinical practice is also recommended in patients with NTG, since PGAs significantly increase the uveo-scleral outflow, without worsening the OBF.

When PGAs fail to reach the target IOP, PGA/beta-blocker combination should be considered. Latanoprost/timolol and travoprost/timolol fixed combinations (LTFC, TTFC) were found effective in lowering the IOP and in reducing the rate of visual field progression in patients with NTG uncontrolled with a single medication. However, in a randomized multi-center 3-month study, TTFC induced a significantly greater IOP reduction compared with LTFC (Shoji et al., 2013).

3.1.2 Laser Therapy

Argon laser trabeculoplasty (ALT) may reduce the IOP by 25% in patients with NTG, even though the effect markedly diminishes over time (Schwartz et al., 1984). Therefore, ALT could be considered as an intermediate step between medical therapy and surgery.

El Mallah et al. (2010) investigated the efficacy of selective laser trabeculoplasty (SLT) in patients with NTG, reporting a significant decrease of both mean IOP and its inter-visit IOP variation. Very recently, Lee et al. (2015) reported that a single session of SLT achieved an additional 20% reduction in IOP with 27% less medication after 6 months compared with baseline. Twelve months after a single session of SLT, the IOP lowering was 15% with 27% fewer eye drops than the prestudy level (Lee et al., 2015). Thus, SLT could be an interesting approach in the management of NTG.

3.1.3 Surgical Therapy

Filtering procedures successfully reduce IOP in patients with NTG: a 30% of IOP lowering from baseline was the most common finding (Abedin et al., 1982; Bhandari et al., 1997; de Jong et al., 1989). In the CNTGS (1998b), a third IOP reduction following trabeculectomy avoided damage progression in 80% of patients.

Recently, the hypothesis of trabeculectomy as an intervention to obtain maximal reduction of the IOP in NTG was studied: it was found that trabeculectomy was a safe and effective method for achieving the target IOP especially in NTG eyes with damage progression at low IOP levels (Schultz et al., 2014). Therefore, surgery should be considered in the event of disease progression despite medical therapy, also in patients with NTG.

3.2 NEUROPROTECTIVE AND VASOACTIVE STRATEGIES

The IOP reduction reduces the progression of all types of glaucoma, including NTG; however, a significant part of patients continues to progress despite a well-controlled IOP (Heijl et al., 2002). Therefore, besides the IOP lowering, different therapeutic approaches are continuously proposed and evaluated in the attempt to stop the optic nerve damage progression. Among all proposed medical strategies, neuroprotection is the most studied area of research in the treatment of glaucoma. Several neuroprotective agents were evaluated even though the results have generally been disappointing. Some of these approaches are already in (limited) clinical use, whereas others are still being investigated (Philip and Kitazawa, 2002).

Recently, *Ginkgo biloba* and anthocyanins were considered a potential adjuvant therapy in NTG patients progressing despite a well-controlled IOP (Cybulska-Heinrich et al., 2012; Shim et al., 2012). *G. biloba* presents antioxidative properties, antiinflammatory and rheological effects, antithrombotic, vasorelaxative and antivasospastic properties, and promotes the stabilization of mitochondria. Furthermore, it has been found that when *G. biloba* is used for other conditions, it may prevent damage progression in NTG.

A role in prevention of visual field impairments in NTG was documented for statins, widely used to lower the plasmatic levels of cholesterol. The systemic administration of statins is effective in reducing the incidence of cerebrovascular and cardiovascular events. Interestingly, it was documented that the use of simvastatin in patients with NTG, who often suffer from vascular diseases, may be associated with visual field stabilization (Leung et al., 2010). Statins also inhibit rho-kinase activity, thus increasing the aqueous outflow and reducing IOP (Hirooka et al., 2006; Nagaoka et al., 2006; Rao et al., 2001).

Previous studies have demonstrated the beneficial effects of calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors in preventing the damage progression in NTG. ACE inhibitor may improve the vascular function by lowering vascular superoxide anion production; thus, it may improve also the vascular circulation of optic nerve head. Moreover, ACE inhibitors have been shown to lower IOP in patients with ocular hypertension or POAG by increasing bradykinin levels and promoting prostaglandin synthesis. Vasospasm has been suggested to play a role in the pathogenesis of glaucomatous damage in patients with NTG. Calcium channel blockers may prevent vasospasm and improve visual field (Kitazawa et al., 1989). Bose et al. (1995) reported an improvement in the contrast sensitivity function after oral administration of nimodipine.

4 SUMMARY AND CONCLUSION

NTG still presents several undefined aspects concerning the pathogenesis and treatment. In the last years, advancements in the knowledge of risk factors have been made, and nonconventional classes of drugs have been studied.

Though the role of IOP in the onset and progression of NTG is still debated, evident changes of the ocular hydrodynamics have been described by using *in vivo* confocal microscopy. Particularly, an activation of the uveo-scleral pathways aimed at regulating the AH outflow and similar to that described in ocular hypertension and POAG seems to be involved also in NTG. Therefore, it is likely that even if IOP falls within the normal range, it could be elevated in eyes with NTG.

The role of the IOP-related mechanical stress has been further supported by the nictemeral monitoring of IOP with contact lens sensor, which showed nocturnal curves and pressure spikes quite similar in POAG and NTG, even though less pronounced in the latter. Also role of the trans-lamina cribrosa pressure has been considered as potential mechanical factors, which may lead to RGC damage in the presence of low levels of cerebrospinal fluid pressure.

To date, the rationale of therapy in NTG is still the IOP reduction (25–30% from baseline), which significantly reduces the rate of progression. However, a consistent proportion of patients continues to progress despite a satisfactory IOP lowering, this highlighting the involvement of additional risk factors in the pathogenesis of NTG. Several studies confirmed the potential role of the autoimmunity as a risk factor for the development of the disease.

In the field of therapy, besides the use of commercially available topical IOP-lowering medications, which represent the gold standard approach, new classes of IOP-independent drugs have been evaluated. Statins seem to improve the OBF and induce a neuroprotective effect on RGC. Also neuroprotective agents, such as *G. biloba*, anthocyanins, and ACE inhibitors are going to be studied, with encouraging preliminary results. Nevertheless, they could represent an important approach in the near future but, currently, have a limited role in the clinical management of glaucoma.

In closing, the clinician must keep in mind that in presence of a rapid progression of the optic nerve damage, an accurate analysis of vascular, immunologic, and metabolic factors is mandatory to evaluate the role of comorbidity on the progression rate of NTG.

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