Abstract: Normal-pressure glaucoma (NPG) is part of the spectrum of the open-angle glaucomas and morphologically characterized, as any glaucoma, by a loss of neuroretinal rim parallel to an enlargement and deepening of the optic cup, and development or enlargement of parapapillary beta zone. These morphological characteristics, in addition to the therapeutic benefit of lowering the intracocular pressure (IOP), make NPG differ from vascular-induced optic neuropathy. Based on the anatomy of the optic nerve as a cerebral fascicle, the physiological counter-pressure against the IOP is the orbital cerebrospinal fluid pressure (CSFP), with both pressures forming the trans-lamina cribrosa pressure difference (TLCPD). In contrast to the IOP, the TLCPD is the true pressure exerting force on the optic nerve fibers when passing through the lamina cribrosa. As a theoretical notion, an abnormally high TLCPD due to a low CSFP, in association with a low arterial blood pressure, could therefore be involved in the pathogenesis of NPG. It fits with the finding that the reduction of the IOP (and thus indirectly of the TLCPD) is (the only proven) procedure for NPG therapy. This review additionally highlights the genetic background, diagnostic methods, and therapeutic modalities of NPG.

Key Words: normal-pressure glaucoma, normal-tension glaucoma, orbital cerebrospinal fluid pressure, trans-lamina cribrosa pressure difference, causes and mechanisms to management

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The term glaucoma includes a panoply of diseases which differ in their etiology, risk factors, demographics, symptoms, duration, therapy, and prognosis. Glaucoma has become one of the most common causes of irreversible blindness worldwide.1,2 From a pathophysiological and therapeutic point of view, IOP is the cardinal modifiable risk factor, as the disease usually stops progressing if the IOP is lowered by 30% to 50% from baseline. It suggests that IOP in glaucoma is too high in relationship to the pressure susceptibility of the optic nerve head where the glaucomatous optic nerve damage occurs.

EPIDEMIOLOGY

Previous studies have reported various primary open-angle glaucoma (POAG) prevalence rates ranging from 0.5%3 to 8.8%4 according to ethnicity, study design, and glaucoma definition. NPG constitutes the major proportion of POAG, which is common in Asian populations.5–7 The POAG prevalence in Asian populations is between 1.0%4 and 3.9%,7 with the proportion of NPG somewhere between 46.9%6 and 92.3%,5 whereas in white and African population studies, the POAG prevalence is between 1.1%10 and 8.8%,4 with NPG proportions ranging from 30.0%11 to 57.1%.12 In a recent review of population-based glaucoma prevalence, the calculated mean proportion of NPG was larger in Asian (76.3%) than in white populations (33.7%).13 To date, the highest NPG proportion reported was 92% from the Tajimi Study5 conducted in Japan, and the lowest was 30% from the Italian Egna-Neumarkt Study.11 Epidemiologic studies have shown that the prevalence of NPG varies considerably depending on ethnicity, with the highest prevalence found in Asian populations. However, within Asian populations, there is also significant variability in the proportion of POAG attributable to NPG. The highest prevalence of NPG has been reported in Japan (Tajimi study, 92%) and Singapore (Singapore Malay Eye Study, 84.6%),14 followed by north China (Handan Eye Study, 83.6%),15 urban south India (Chennai Glaucoma Study, 82%),16 south China (Liwan Eye Study, 79.3%), and South Korea (The Namil Study, 77%).17 There are some minor differences in proportion of NPG among white POAG populations. It is 38.9% in the Rotterdam Study from the Netherlands,18 31.7% in the Beaver Dam Eye Study from the United States,19 31.0% in the Reykjavik Eye Study from Iceland,18 and 30% in the Egna-Neumarkt Study from Italy.11 For the African populations, it is 57.1% in a rural district in South Africa,12 and about 30% in the Barbados Eye Study from North America,10 suggesting that the prevalence of NPG is lower in African populations than in the Asian population.

Whether the increased prevalence of NPG in Asian populations is due to genetics or environment is a question that remains to be answered. But epidemiologic and genetic studies suggest that patients with NPG have a different set of predisposing risk factors compared with patients with high-tension POAG. Patients
with NPG tend to be older than patients with POAG. Female subjects have a higher prevalence of the disease than male counterparts. Several studies showed a thinner mean central corneal thickness in patients with NPG. Systemic vascular diseases are known risk factors of NPG, including migraine, systemic low blood pressure, low diastolic ocular perfusion pressure, Alzheimer disease, and others. Some studies demonstrated that an association between myopia and glaucoma was stronger at lower IOP levels, and the association weakened with increasing IOP, indicating that myopia is an important risk factor, particularly for NPG. Systemic vascular diseases were more common, and prevalence of myopia is high in Japanese and Chinese populations, which perhaps could explain the high prevalence of NPG in these populations. Pekmezci et al have reported that Japanese Americans also have a high prevalence of NPG, suggesting that the increased risk of NPG is at least in part due to genetic factors.

It should be noted that the proportion of NPG among POAG in glaucoma clinics or managed care networks was much lower than that in the population, showing that NPG may be under-diagnosed. The percentage of NPG among POAG was reported at 0.76% in Tongren Hospital, Beijing, 10.8% in a national managed care network in the United States (2001–2007), 26.5% in Hong Kong Eye Hospital and the Eye Clinic of the Prince of Wales Hospital, 23.5% in central Sweden, 6.3% in west Africa, and 5.5% in Iceland. Overall, the percentage of NPG among patients with POAG in glaucoma clinics is roughly <30% worldwide. This issue of underdiagnosis is a worldwide problem. Public education and regular eye examinations may be helpful for early detection and prevention of disease progression toward blindness, especially to those with high risk factors and in high prevalence countries.

**ETIOLOGY, CAUSES, AND MECHANISMS**

Despite the marked heterogeneity of the panoply of the glaucomas, the IOP is the (only) modifiable risk factor, the reduction which is therapeutically useful in any type of the glaucoma including NPG. It suggests that the IOP in glaucoma is too high in relation to the pressure susceptibility of the optic nerve head where the glaucomatous optic nerve damage occurs. The common denominator of all glaucoma forms is the loss of retinal ganglion cells, thinning of the retinal nerve fiber layer (RNFL) and in particular, cupping of the optic disc. Many glaucomatous eyes often additionally show an enlarged parapapillary beta zone. Eyes with non-glaucomatous optic nerve damage due to vascular or other reasons, and eyes with glaucomatous optic neuropathy have the loss of retinal ganglion cells and the subsequent thinning of the RNFL in common. Both groups differ in the loss of neuroretinal rim and subsequent optic disc cupping, which are almost pathognomonic for the glaucomas. Besides in eyes with glaucoma, optic disc cupping is observed otherwise only in eyes after an arteriitic anterior ischemic optic neuropathy in which the occlusion of the posterior ciliary arteries may lead to an infarct of the lamina cribrosa resulting in a destruction of the latter and allowing the vitreous (hyaluronic acid) to enter the retrolaminar optic nerve tissue. A similar histopathologic finding has been reported for Schnabel cavernous optic nerve damage in eyes after very high IOP elevation, and in which the vitreous (hyaluronic acid) is pressed through the lamina cribrosa into the retrolaminar optic nerve tissue. The clear morphological distinction between glaucomatous optic neuropathy with optic disc cupping (and parapapillary beta zone) and non-glaucomatous, vascular-induced optic nerve damage with a preservation of the shape of the optic cup, increased pallor of the remaining neuroretinal rim, and no markedly enlarged beta zone contradicted considering a vascular insufficiency as primary cause for glaucomatous optic nerve fiber loss, including NPG.

In many patients with glaucoma, the IOP as the most important risk factor is only slightly elevated or within the statistically normal range. When addressing the question, why can a statistically normal IOP still be so high in eyes with NPG, one may consider several aspects. The pressure susceptibility of the optic nerve head may be influenced by local tissue factors, biomechanical parameters, and forces and pressures which in addition to the IOP present in the region of the optic nerve heads. It is the lamina cribrosa where the damage to the retinal ganglion cell axons or optic nerve fibers occurs in glaucoma. The lamina cribrosa forms the pressures-shed between the intracranial compartment with the IOP and the retro-lamina compartment with the optic nerve tissue pressure and retrobulbar CSFP. The difference between the IOP and the retrobulbar CSFP as counter-pressure against the IOP is called TLCPD. From an anatomical and pathophysiological point of view, it is this TLCPD which exerts a force onto the lamina cribrosa, whereas the IOP is just the trans-corneal pressure difference and is thus only 1 of the 2 determinants of the TLCPD. This relationship raises the possibility that eyes with NPG have a normal trans-corneal pressure difference (ie, IOP) and an abnormally low retrobulbar CSFP, thus the TLCPD is elevated. Under this condition, a pressure-related (barotraumatic) damage to the optic nerve fibers when passing through the lamina cribrosa could occur in the presence of a normal IOP. The barotraumatic mechanism in NPG could also explain the similar appearance of the optic nerve head in eyes with high-pressure glaucoma and eyes with NPG.

Clinical and experimental investigations have supported such hypothesis. Studies revealed that a higher CSFP is related to younger age, higher blood pressure, and higher body mass index. These relationships might explain why in Japan, as shown in the Tajimi Study, the prevalence of NPG was relatively high, with Japanese patients with NPG being elder and slim, and having a low arterial blood pressure. In contrast, glaucoma patients in North America have a higher body mass index and higher arterial blood pressure, parallel to a lower prevalence of NPG. A surrogate for the intraorbital CSFP is the width of the orbital CSF space around the optic nerve. In a clinical study, the width of the orbital CSF space as measured by magnetic resonance imaging was smaller in patients with NPG than in glaucoma patients with high IOP, and it was also smaller in normal individuals after adjusting the diameter of optic nerve. In another clinical study, the CSFP as measured by lumbar puncture was lower in patients with NPG than in glaucoma patients with high IOP or patients without glaucoma. In an experimental study, monkeys with artificial reduction of their CSFP developed optic nerve damage, although it remained unclear whether this damage was also accompanied by optic disc cupping as hallmark of glaucomatous optic neuropathy.

It may be further considered that the IOP and its counter-pressure, the orbital CSFP, are not constant and they fluctuate in dependence of the cardiac cycle. In an experimental study,
Morgan et al observed that the spontaneous pulsation of the central retinal vein, which can be seen in about 80% to 90% of normal eyes, was associated with a phase shift of the pressure wave in the orbital CSFP space versus the intraocular compartment. He concluded that the systolic pressure wave, coming from the heart, first arrived in the brain and orbital CSF space, and a bit later in the eye. The pressure increased in the orbital CSFP space, pushing the venous blood back into the eye (and leading to a dilation of the central retinal vein), before it increased in the eye eventually; whereas the pressure decreased again in the orbital CSF compartment. This shift in the pressure waves of the retro-laminar CSF compartment and the prelaminar intraocular compartment leads to a pulse-synchronous fluctuation of the TLCPD. Theoretically, this fluctuation physiologically may be necessary to facilitate the retrograde axoplasmic flow entering the eye (during the high-CSFP phase) and to facilitate the orthograde axoplasmic flow leaving the eye (during the high-IOP phase). If this notion is valid, any change in the temporal relationship between the CSF pressure wave and IOP wave, even in the presence of normal values of the IOP and CSFP, could lead to a damage to the optic nerve fibers.

A special situation may be present in highly myopic eyes with optic nerve damage. Hospital- and population-based studies have shown that highly myopic eyes as compared with nonhighly myopic eyes have a significantly higher prevalence of glaucomatous or glaucoma-like optic neuropathy. The cutoff value of the myopic eyes have a significantly higher prevalence of glaucomatous or glaucoma-like optic neuropathy increased 26.0 to 26.5 mm. With increasing axial elongation, the prevalence of glaucomatous or glaucoma-like optic neuropathy increased curvilinearly, with a prevalence of > 50% in the axial length range of > 30 mm. This optic neuropathy in high myopia is characterized by an often normal IOP and by a kinking of the intra-papillary blood vessels close to the optic disc border. The vessel kinking indicates a loss of neuroretinal rim so that the morphological definition of glaucomatous optic nerve damage would be fulfilled. As studies which show that a reduction of the IOP in these eyes is therapeutically useful are missing, it has remained unclear whether this type of optic neuropathy with optic disc cupping is glaucomatous or glaucoma-like. The reason for the increased prevalence of glaucomatous or glaucoma-like optic nerve damage in highly myopic eyes may be manifold. The myopic axial elongation takes place predominantly in the posterior half of the globe. It leads to an enlargement of the optic disc with secondary elongation and thinning of the lamina cribrosa. The thinning of the lamina cribrosa reduces the distance between the intraocular compartment with the IOP and the retrolaminar compartment with the CSFP, thus the pressure gradient across the lamina cribrosa steepens. This phenomenon, in addition to morphological changes inside of the lamina cribrosa due to its elongation and stretching, may be one of the reasons for the increased susceptibility of optic nerve damage in high myopia. Morphological changes in the parapapillary region in highly myopic eyes include the development of gamma zone defined as the region without Bruch membrane, and an elongation and thinning of the peripapillary scleral flap, namely the delta zone. The peripapillary scleral flap acts as the biomechanical anchor for the lamina cribrosa so that its stretching will affect the biomechanics of the lamina cribrosa. Accordingly, studies suggested that the risk of a glaucomatous or glaucoma-like optic neuropathy in highly myopic eyes was higher with a larger optic disc size and/or a larger parapapillary delta zone.

Interestingly, some highly myopic eyes show an absolute central scotoma, although the macula exhibits only a category 2 of myopic maculopathy with an intact Bruch membrane, choriocapillaris and retinal pigment epithelium, and normal deep retinal layers in the absence of a glaucomatous or glaucoma-like intrapapillary vessel kinking close to the optic disc border. The explanation for the perimetric and vision loss in these eyes may be a nonglaucomatous optic nerve damage caused by the myopia-related increase in the fovea-disc distance due to the development and enlargement of parapapillary gamma zone. The increased fovea-disc distance may lead to a stretching of the retinal ganglion cell axons with eventual loss of these optic nerve fibers.

Apart from the whole panoply of potential anatomical and other risk factors for glaucomatous optic neuropathy, the only proven therapeutic method to prevent the development or progression of glaucoma is the reduction in IOP. It is valid for glaucomatous eyes with elevated IOP and for eyes with NPG. It speaks in favor of a common, that is barotraumatic, pathogenesis of glaucoma with IOP and for NPG.

The IOP, or better speaking the TLCPD, can cause mechanical stress and strain on the lamina cribrosa leading to a compression, deformation, and eventual remodeling of the lamina cribrosa with consequent mechanical axonal damage, and disruption of the orthograde and retrograde axonal transport. The disruption of the retrograde axoplasmic flow decreases the delivery of trophic factors from the neurons of the lateral geniculate nucleus to the retinal ganglion cell bodies in the retina.

A low ocular perfusion pressure including a low systemic blood pressure has also been found to be associated with glaucomatous optic neuropathy. Ocular perfusion pressure has been estimated as two thirds of the systolic blood pressure minus the IOP (as surrogate for retinal venous pressure). However, one may wonder whether the relation between lower ocular perfusion pressure and POAG is driven mostly by higher IOP. An additional limitation in the assessment of the ocular perfusion pressure is that the increased retinal venous blood outflow resistance in glaucoma leads to an increased retinal vein blood pressure which is higher than the IOP. Taking the IOP as surrogate for retinal venous blood pressure may therefore lead to an overestimation of the ocular perfusion pressure. A contraargument against a low ocular perfusion pressure being the cause for optic nerve damage in NPG is that all known vascular optic neuropathies (except for giant cell arteritis-induced optic nerve damage) do not lead to an optic disc cupping which is a hallmark of glaucomatous optic neuropathy in eyes with high IOP and in those with normal IOP. The potential association between low arterial blood pressure and NPG could perhaps also be explained by the relationship between low arterial blood pressure and low CSFP. In general, an overtreatment of systemic arterial hypertension and nocturnal arterial hypotension should be avoided, and medications lowering arterial blood pressure may preferentially be applied in the morning instead of the evening.

It has remained unclear whether the mitochondria located in high concentration within the axons in the prelamina region play a direct role in the pathogenesis of glaucomatous optic neuropathy. In a similar manner, the pathways from gene mutations contributing to glaucoma and the eventual dysfunction of the proteins...
GENETICS

POAG is a group of complex diseases resulted from the interaction of multiple genetic and environmental risk factors. NPG being a continuum of POAG is also multifactorial in etiology. The segregation in pedigrees suggests the involvement of genetics in NPG. However, when comparing with high-tension glaucoma (HTG), NPG pedigrees have been relatively less reported in the literature, suggesting that the genetic architecture of NPG can be more complex. In the past 2 decades or so, efforts have been made to identify disease genes for POAG, HTG, and/or NPG in different populations using linkage analysis, candidate gene mutational screening, candidate gene association analysis, copy number variation analysis, and genome-wide association analysis. Furthermore, genetic components have been compared between HTG and NPG to identify the similarities and differences between the 2 glaucoma subtypes.

Linkage analysis using microsatellite markers in disease pedigrees is the earliest genetic approach to mapping the genetic loci that may contain the disease-causing gene for a particular disease. The first genetic locus mapped for POAG was the GLC1A locus located at chromosomal region 1q23-q25. To date, 17 genetic loci have been linked to POAG, namely GLC1A to GLC1Q, with details documented in OMIM (Online Mendelian Inheritance in Man, https://www.omim.org/) and HGNC (HUGO Gene Nomenclature Committee, https://www.genenames.org/). Of note, these loci were mostly mapped in pedigrees with HTG. Regarding NPG, the first specific locus was mapped to the 10p15-p14 region (GLC1E) in a British family with NPG. Moreover, the GLC1B locus at the 2cen-q13 region was mapped in patients with low to moderate IOP (11–34 mm Hg). These linkage loci helped narrow down the genomic regions for further identification of disease-causing genes and mutations for POAG and NPG.

Each linkage locus contains a large number of genes. Thus, further genetic fine mapping is needed to pinpoint the disease-causing genes and mutations in the POAG loci, mainly through sequence analysis of candidate genes. Mutational screening analysis of the GLC1A locus had led to identification of the myocilin (MYOC) gene for POAG. Subsequently, larger-scale cohort-based mutational screening studies had identified more disease mutations in MYOC, enabling genotype-phenotype correlation analysis in POAG. MYOC mutations were identified in patients ranging from juvenile glaucoma to typical late-onset POAG, with maximal recorded IOP ranging from 12 to 77 mm Hg. In a more recent study, the p.Gln368Ter mutation in MYOC was identified in both NPG and HTG patients. Therefore, although MYOC was considered a gene prominently for HTG, it should also play a role in NPG. Further studies are needed to elucidate the role of MYOC in IOP elevation and optic nerve damage. Regarding the GLC1E locus, the optineurin (OPTN) gene was identified as the causal gene, where mutations were prominently identified in NPG, although some were also identified in HTG. Similarly, mutations in the WDR36 gene at GLC1G were identified in both HTG and NPG patients. In the GLC1B locus, the NCK2 gene was suggested as a candidate gene for NPG. However, definitive support for NCK2 as a causal gene for NPG from mutational screening and familial segregation analysis is still lacking. Therefore, existing evidence suggests that HTG and NPG may share certain common genetic components.

Although several causal genes at the linkage loci of POAG have been identified, these genes together contribute to a small proportion of patients. Therefore, a large proportion of POAG should have resulted from multiple genetic and environmental susceptibility factors. So far, a number of candidate genes for POAG have been identified by association studies. The selection approaches for candidate genes varied among different studies, mainly including genes that are located in known linkage loci for POAG, genes that are causative for POAG (such as MYOC and OPTN), genes that are involved in potential biological pathways of glaucoma, or genes that are associated with a similar disease such as optic atrophy. Single-nucleotide polymorphisms (SNPs) are commonly used in association analysis. SNPs in MYOC have been associated with POAG and ocular hypertension, and NPG. Similarly, SNPs in OPTN have also been associated with both HTG and NPG. The optic atrophy 1 (OPA1) gene, the gene responsible for autosomal dominant optic atrophy, has been associated mainly with NPG, but also with HTG. In a meta-analysis, significant association between both OPA1 polymorphisms and NPG was found in whites but not in Asians, suggesting ethnic diversities. This study also showed that OPA1 polymorphisms were not associated with HTG. Therefore, the OPA1 gene is more likely to be a susceptibility gene for NPG. However, further studies are warranted to confirm its role in both NPG and HTG in different ethnic populations. Apart from single point variants, copy number variations have also been implicated in POAG, including NPG. Copy number variations on chromosome 12q14, a region previously mapped as GLC1P, have been associated with NPG, where an extra copy of the encompassed TBK1 gene is likely responsible for glaucoma.

To date, a number of candidate genes have been implicated in POAG (including NPG); however, the roles of many candidate genes remained inconclusive because candidate gene studies were usually limited by small sample sizes, lack of replication cohorts, and/or limited gene coverage by selected SNPs. With the advent of genome-wide association study (GWAS), which is a hypothesis-free approach involving SNPs across the entire genome, a large number of genetic loci for POAG have been identified and validated in different ethnic groups. Currently, >10 GWASs have been reported for POAG. However, most of these GWASs were initially conducted in POAG, and only 1 GWAS was conducted initially in NPG (Table 1). Interestingly, in some of these GWASs where HTG and NPG were stratified, the odds ratios for the major SNPs in both HTG and NPG were all toward the same directions, including FMLN2, PED7B, TMT2, FNDC3B, ANKR355-MAP3K1, LMX1B, LHPP, HMG2A, MEIS2, LOX11, ABCA1, PM2M, and S1X6 (Table 1). These data suggested that HTG and NPG should have shared a large proportion of genetic susceptibilities. Whole-exome and whole-genome sequencing analyses are new and powerful platforms for identifying disease-causing and -associated genes. Further large-scale genome-wide studies on NPG, and comparisons between NPG and HTG should lead to discovery of new genetic loci for NPG, and loci that may distinguish NPG from HTG.
| Gene/Loci | Study Population | Glaucoma subtype in GWAS | Representative SNP* | Effect Allele | POAG | HTG | NPG | Reference |
|-----------|-----------------|--------------------------|----------------------|---------------|------|-----|-----|-----------|
| EXOC4     | African          | POAG                     | rs141186647          | A             | 1.04 | N/A | N/A | Bonnemaijer et al. Hum Genet. 2018 |
| FMNL2     | Multiethnic§    | POAG                     | rs56117902           | A             | 0.88 | 0.86 | 0.99 | Choquet et al. Nat Commun. 2018 |
| PDE7B     | Multiethnic‡    | POAG                     | rs9494457            | T             | 1.16 | 1.18 | 1.07 |          |
| near TMTC2| Multiethnic‡    | POAG                     | rs324794             | G             | 0.87 | 0.88 | 0.83 |          |
| near IKZF2| Multiethnic     | POAG                     | rs5633522            | G             | 1.18 | N/A | N/A |          |
| CADM2     | Multiethnic‡    | POAG                     | rs34201102           | A             | 1.11 | N/A | N/A |          |
| near DKGK | Multiethnic‡    | POAG                     | rs9853115            | T             | 1.11 | N/A | N/A |          |
| ANKH      | Multiethnic‡    | POAG                     | rs76325372           | A             | 1.14 | N/A | N/A |          |
| EXOC2     | Multiethnic‡    | POAG                     | rs2073066            | C             | 0.86 | N/A | N/A |          |
| LMX1B     | Multiethnic‡    | POAG                     | rs55770306           | C             | 0.86 | N/A | N/A |          |
| FND3C3B   | Japanese        | POAG                     | rs7636836            | T             | 1.12 | 1.2  | 1.08 | Shiga et al. Hum Mol Genet. 2018 |
| ANKRD55-MAP3K1 | Japanese   | POAG                     | rs61275591           | A             | 1.13 | 1.23 | 1.14 |          |
| LMX1B     | Japanese        | POAG                     | rs10819187           | G             | 1.21 | 1.19 | 1.18 |          |
| LHPP      | Japanese        | POAG                     | rs12262706           | G             | 1.11 | 1.15 | 1.15 |          |
| HMG4A2    | Japanese        | POAG                     | rs343993             | G             | 1.11 | 1.12 | 1.05 |          |
| MIR22     | Japanese        | POAG                     | rs28480457           | C             | 1.14 | 1.08 | 1.25 |          |
| LOXL1     | Japanese        | POAG                     | rs1048661            | T             | 1.13 | 1.10 | 1.19 |          |
| near FOXC1| Caucasian       | POAG                     | rs2745572            | A             | 1.23 | N/A | N/A | Bailey et al. Nat Genet. 2016 |
| ATXN2     | Caucasian       | POAG                     | rs7137828            | T             | 1.18 | N/A | N/A |          |
| TXNRD2    | Caucasian       | POAG                     | rs35934224           | T             | 0.77 | N/A | N/A |          |
| near TGFBR3| Multiethnic‡  | CAUCASIAN (US and AU)    | rs1192415            | G             | 1.13 | N/A | N/A | Li et al. Hum Mol Genet. 2015 |
| ABCA1     | Chinese         | POAG                     | rs2487032            | A             | 0.73 | 0.71 | 0.77 | Chen et al. Nat Genet. 2014 |
| PMM2      | Chinese         | POAG                     | rs3785176            | G             | 1.30 | 1.30 | 1.28 | Gharakhani et al. Nat Genet., 2014 |
| AFAP1     | Australian      | POAG                     | rs4619890            | G             | 1.20 | N/A | N/A |          |
| GMDS      | Australian      | POAG                     | rs11969985           | G             | 1.31 | N/A | N/A | Wiggs et al. PLoS Genet. 2012 |
| SIX6      | European (US)   | POAG                     | rs10483727           | A             | 1.32 | 1.31 | 1.33 | Burdon et al. Nat Genet. 2011 |
| TMCO1     | Australian      | POAG                     | rs4656461            | G             | 1.51 | N/A | N/A |          |
| CDKN2BAS  | Australian      | POAG                     | rs4977756            | A             | 1.39 | N/A | N/A | Thorliefsson et al. Nat Genet. 2010 |
| CAV1/CAV2 | European (Iceland) | POAG                     | rs4236601            | A             | 1.36 | N/A | N/A |          |
| SRBD1     | NPG             | POAG                     | rs3213787            | A             | N/A | N/A | 2.80 | Writing Committee for the Normal Tension Glaucoma Genetic Study Group of Japan Glaucoma Society. Ophthalmology. 2010 |
| ELOVL5    | Japanese        | NPG                      | rs735860             | C             | N/A | N/A | 1.69 |          |

AU indicates Australian; GWAS, genome-wide association study; HTG, high-tension glaucoma (IOP >21 mm Hg); NPG, normal-pressure glaucoma (IOP ≤21 mm Hg); POAG, primary open-angle glaucoma; SNP, single-nucleotide polymorphism; US, United States.

*Representative SNP indicates the SNP that had the strongest association (in terms of P value) with the glaucoma subtype involved in the GWAS phase.

†POAG indicates mixed HTG and NPG if indicated in the articles, or patient group in which the IOP was not specified.

‡Multiethnic, multiple ethnic groups including non-Hispanic white, Hispanic/Latino, East Asian, African-American, European, South Asian, African British, and mixed ancestries.

§Multiethnic, multiple ethnic groups from Beijing, Hong Kong, Japan, Singapore, South India, Vietnam, Australia (ANZPAG), Shanghai, Chengdu, Shantou, France, Germany, Korea, Malaysia, Saudi Arabia, UK, USA-African Americans, USA GLAUGEN, USA MEEI, USA NEIGHBOR.
DIAGNOSIS

Since the first description of “amaurosis with excavation” by von Graefe in 1857 and his proposal that glaucoma could occur without an elevation of IOP, the etiology of NPG has remained enigmatic. NPG is understood as a form of open-angle glaucoma (OAG) with characteristic excavated optic disc and glaucomatous visual field (VF) loss, despite an IOP that is persistently within a statistically normal range (ie, <21 mm Hg). The diagnostic criteria of NPG are generally adapted as per the Collaborative Normal Tension Glaucoma Study (CNTGS), which included 6 median untreated IOP readings consistently <21 mm Hg, with no >1 reading equal to 23 or 24 mm Hg and no single measurement >24 mm Hg, and at least 2 readings were obtained at a different time of the day from the rest; drainage angle of Shaffer grade II or above on darkroom gonioscopy; glaucomatous optic disc cupping and loss of neuroretinal rim; and fulfilling the minimal criteria for glaucomatous VF defect [glaucoma hemifield test result outside normal limits, pattern standard deviation with \( P < 0.05 \) or a cluster of \( \geq 3 \) points in the pattern deviation plot in a single hemifield (superior or inferior) with \( P < 0.05 \) of which must have \( P < 0.01 \). Any one of the preceding criteria, if repeatable, was considered sufficient evidence of a glaucomatous VF defect].

The criteria served to rule out other causes of optic neuropathy, to confirm the diagnosis of glaucoma and to rule out other glaucoma subtypes. Gonioscopy must always be performed to rule out angle closure. The morphology of optic disc must be carefully observed to rule out other causes of optic neuropathy. The cup-disc ratio should be carefully documented. Measurement of vertical cup-disc ratio could affect the prediction of glaucoma progression, especially if a previously suggested risk assessment scheme is applied. Furthermore, the vertical cup-disc ratio (VCDR) measured by other instruments [eg, optical coherence tomography (OCT)] should not be interchangeable with the VCDR measured by clinical examination. Indeed, previous study reviewed poor agreement of VCDR measured by different techniques and that could affect risk assessment in ocular hypertensive patients. As a general rule, it is required to have at least two VF to confirm a VF defect instead of solely relying on VF results, given the known variability of VF performance.

It is important to note that NPG is a diagnosis by exclusion. We should evaluate the patient thoroughly with the aim of distinguishing NPG from POAG and other differential diagnoses, and investigating other conditions associated with NPG. During history taking, clinician should specifically enquire other related systemic medical conditions (Table 2), history of ocular trauma or surgery (including refractive surgery), family history of glaucoma, and medication being taken by the patient. Ophthalmologic examination should include best-corrected visual acuity, color vision test, pupillary examination, Goldmann applanation tonometry, pachymetry for central corneal thickness, dark-room gonioscopy, and 24–2 standard automated perimetry. Some authors also suggested that the standard 10–2 strategy should be included as part of the routine examination because the 24–2 strategy could miss out important central VF defect, especially in early-stage RNFL damage. Apart from the detail evaluation of the optic nerve head by clinical examination and fundus photography, OCT should be fully utilized to evaluate and document the status of the optic nerve head, RNFL, and ganglion cell complex. Diurnal IOP measurement or 24-hour IOP (the latter is more difficult in clinical practice) should be obtained to confirm the persistently low IOP status. Other adjunctive tests for IOP such as water provocative test and dilatation provocative test were mentioned in other literature. However, they are out of the scope of this article and are largely of historical value.

When making the diagnosis of NPG, we should also be aware of other differential diagnoses listed in Table 3, together with the specific differentiating tests. There is no evidence to support a routine neuroimaging evaluation for all NPG patients. However, it is worth considering in certain clinical scenarios such as young age with significant reduction of visual acuity, new onset or worsening of headache, other neurological symptoms apart from migraine, atypical VF defect (eg, VF that respects the vertical midline, lack of structural-functional correlation), reduction in or loss of color vision, paller of the neuroretinal rim, and highly asymmetric cupping, moderate to severe visual field loss.

It is possible that NPG can be a manifestation of other general medical conditions associated with NPG. NPG is also known for its higher incidence of disc hemorrhage (DH) compared with POAG. When DH is identified, rather than immediately relating to NPG, one should also consider other causes of DH, including posterior vitreous detachment, optic disc drusen, other causes of optic neuropathies, diabetic retinopathy, and vascular occlusive disease.

Despite a persistently lower level of IOP, NPG shares similar features of optic nerve damage compared with the higher-tension POAG. It is generally agreed that there is considerable overlap between NPG and POAG. The 2 diseases represent a continuum of OAGs, in which IOP is the predominant pathogenic factor in the higher-tension POAG, whereas other factors in addition to IOP are also important in NPG. This might explain their differences in VF defect and structural abnormalities. VF of NPG patients showed significantly deeper and closer-to-fixation scotoma. NPG patients also had a higher percentage of abnormal points in the upper and lower central retina. Structural changes, apart from the above-mentioned higher incidence of DH in NPG patients, they also tend to have a larger and deeper optic disc cupping, and a less well-defined, saucerized, and thinner neuroretinal rim, particularly in the temporal and inferior zones. NPG patients also have a more localized loss of macular ganglion cell complex in the inferior hemifield, compared with the more diffused loss in high-pressure POAG patients. Enhanced depth imaging OCT reviewed that the prelamellar tissue was significantly thinner in the POAG group.
Don't have a concrete evidence to favor treatment for preperimetric disease. Against this background, OCT should be routinely used for the early invention and a higher likelihood of preventing visual loss.

One of the difficulties of managing NPG is that, although the CNTGS study showed that a 30% IOP reduction slowed the disease progression, and the outcomes for individual patients were highly variable.73 In the study, 20% of the treated patients experience continuous deterioration. However, more than half of the untreated patients have a static course over 5 to 7 years. This may reflect that factors other than IOP (IOP-independent factors) play a role in the pathogenesis of the disease. Pressure-cornea-vascular index, an index that put vascular risk factors into consideration, was suggested to be a tool to predict disease progression for individual NPG patients.74 This may provide a reference for the clinician to establish a more tailor-made treatment strategy for individual patients, although validation of pressure-cornea-vascular index with another NPG cohort is necessary.

IOP-Dependent Factor

**Medications**

IOP control remains one of the most important modifiable risk factors for all types of glaucoma.

The treatment of NPG anchors on the fundamental CNTGS designed in 1985. The study showed that a 30% reduction by either medications or laser trabeculoplasty reduced the risk of Humphrey VF progression to 12% at 5 years as compared with 35% in the nontreatment group.69 Around 57% of the patients were able to achieve the 30% target IOP with medications and/or laser trabeculoplasty.68 The commonly utilized antiglaucoma medications (prostaglandin analogues, alpha-2 agonists, beta-blockers, carbonic anhydrase, and cholinergics) may be used monotherapy, in combination or as fixed-combination regimens. The Low-pressure Glaucoma Treatment Study from 2011 determined that patients treated with brimonidine 0.2% had less VF worsening (9%) as compared with those treated with timolol 0.5% (39%), despite similar levels of IOP control in both groups.89 It is debatable whether the difference in outcome was due to the neuroprotective effect of brimonidine or the detrimental systemic hypoperfusion effect from timolol. In general, nonselective topical beta-blockers are avoided in the evening for this reason. However, the trial has received criticisms of having a higher dropout rate in the brimonidine group, improper handling of missing data, and exclusion of subjects after randomization.

**MANAGEMENT**

One of the difficulties of managing NPG is that, although the CNTGS study showed that a 30% IOP reduction slowed the disease progression, and the outcomes for individual patients were highly variable.73 In the study, 20% of the treated patients experience continuous deterioration. However, more than half of the untreated patients have a static course over 5 to 7 years. This may reflect that factors other than IOP (IOP-independent factors) play a role in the pathogenesis of the disease. Pressure-cornea-vascular index, an index that put vascular risk factors into consideration, was suggested to be a tool to predict disease progression for individual NPG patients.74 This may provide a reference for the clinician to establish a more tailor-made treatment strategy for individual patients, although validation of pressure-cornea-vascular index with another NPG cohort is necessary.
Although alpha-adrenergic receptor agonists (brimonidine, apraclonidine) reduce the neurotoxic effects of glutamate, paradoxically, alpha-adrenergic receptor antagonists (bunazosin hydrochloride) are also neuroprotected by counteracting the effects of endothelin-1, glutamate, and nitric oxide.91

Animal models have shown that β-blockers (betaxolol, timolol, and levobetaxolol) may also have neuroprotective effects via the regulation of calcium channels or expression of neurotrophic factors.92 Similarly, prostaglandin analogues may also exert a neuroprotective effect on the retina from animal models.93 Kashiwagi et al treated NPG patients with latanoprost monotherapy and reported that after 5 years, 68% of patients had no glaucoma progression,94 although the CNTGS study found that half of untreated NPG patients did not have further VF loss after 5 years.88

Rho kinases (ROCK1 and ROCK2) possess multiple modes of actions for glaucoma control: IOP-lowering, antiglaucoma properties, and induction of axonal regeneration. Rhopressa (netarsudil 0.02%) is a new class of dual-therapy eye drop that increases aqueous outflow and decreases aqueous inflow. Even the newer Roclatan (netarsudil with latanaprost) is likely to further reduce IOP by reducing aqueous production and increasing outflow through the trabecular meshwork and uveoscleral pathways.95

Laser Trabecuoplasties

Selective laser trabeculoplasty (SLT) has largely replaced argon laser trabeculoplasty due to SLT’s scarless and repeatable properties. The Laser in Glaucoma and Ocular Hypertension study found that at 36 months, 74.2% SLT treated patients remained medication-free. Even though there was no significant difference in quality of life scores between the medication and SLT groups, SLT seemed to be more cost-effective. Usually, treatment involves confluent laser spots to 360 degree trabecular meshwork with a starting energy of 0.8 mJ and titrated until champagne bubble formation is seen. Lee et al reported that a single session of SLT as adjuvant treatment for NPG achieved an additional 15% IOP reduction when using 27% less medication at 1 year compared with prestudy levels.96 A higher preSLT IOP is one of the most reliable predictors of success for SLT; thus, the amount of IOP reduction is expected to be less than that for high pressure POAGs. The success rate of SLT for NPG (defined as IOP reduction ≥20% from baseline) has been reported to be around 60%.71 The newer MicroPulse laser trabeculoplasty produces similar results as SLT but with less postlaser anterior chamber reaction and less intraoperative pain due to the 15% duty cycle technology of MicroPulse laser trabeculoplasty.95

Surgeries

Due to a preexisting IOP ≤21 mm Hg and a target reduction of only 30%, surgery is not often required for NPG, although it may be considered for those with inadequate IOP control with maximal tolerable topical medications, nonresponders to laser trabecuoplasties, or for those selected patients who wish to be medication-free. Modifications from conventional trabeculotomy techniques are suggested to avoid overfiltration including the judicious use of intraoperative mitomycin C, tighter scleral flap sutures, and leaving behind some viscoelastics in the anterior chamber. Minimally invasive glaucoma surgeries such as EX-PRESS shunt or canaloplasty may also achieve the target IOP reduction but with less sight-threatening complications than trabeculectomy.96 Ab-internal procedures such as stents, Trabectome, or Kahook dual blade may also be considered for those receiving concomitant cataract extractions, but bearing in mind the amount of IOP reduction will be limited by the episcleral venous pressure and hence hypotony will also be less likely. Newer modalities such as Xen and MicroPulse transscleral cyclophotocoagulation may also offer less invasive alternatives, although more clinical trials are warranted to support their actual efficacy and safety in NPG.

IOP-Independent Factors

Although NPG falls within the spectrum of OAG, adequate IOP control may not be enough for NPG patients in slowing down disease progression. Systemic cardiovascular stability and neuroprotection are key components.

Neuroprotection

As glaucoma is an essential damage to the retinal ganglion cells, saving and repairing damaged neurons is only a logical approach. However, the quest for neuroprotective agents has not been straightforward because of uncertainties and limitations in clinical functional endpoints, disease pathogenesis, and animal models required for research. The relatively slow rate of disease progression also makes clinical trials a high investment risk for pharmaceutical companies. In 2008, research on an emerging NMDA receptor antagonist, memantine, was terminated after phase III trials due to a lack of significant results compared with placebo.67 Ongoing research is investigating various biochemical pathways and pharmaceutical agents that may be beneficial to retinal ganglion cell survival including the following potential agents: purinergic receptors, KATP channels (inward-rectifying potassium channels), gaseous agents (nitric oxide, carbon monoxide, hydrogen sulphide), nonglucocorticoid steroidal compounds (estrogen), phosphoinositoide 3-kinase/Akt activators, citicoline, histone deacetylase, dopaminergic receptors agonist, cannabinoids, and small interference-RNAs.93

Hypoperfusion

Insufficient or imbalanced blood flow to the optic nerve leads to ischemic-reperfusion injuries. Systemic diseases leading vascular dysregulation of the optic nerve require joint care from an internal medicine physician including migraine, Raynaud disease, obstructive sleep apnea, anemia, heart failure, transient ischemic attacks, cardiac arrhythmias, hypertension and hypotension especially nocturnal hypotensive dips.20 Those with systemic hypertension on oral medications may consider a morning regimen to avoid excessively low blood pressures during the night. As for the choice of antihypertensive medications, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers may also confer a potential neuroprotective effect by increasing bradykinin levels which in turn protect retinal cells and increase prostaglandins that enhance aqueous outflow.94 Concomitant use of statins for hyperlipidemia and metformin for diabetes may also offer protection against NPG by possibly reducing glutaminergic neurotoxicity and apoptosis.24

Whilst anticonvulsants like valproic acid have been found in animal models to lower glaucomatous damage as marked by less ganglion cell death and less retinal nerve layer thinning, its
effect in vivo studies has yet to be determined and its use in NPG must be balanced by the potential systemic side effects of the drug for those without seizure symptoms.91

Apart from prevention, brain-derived neurotrophic factor has been shown in animal models to play a role in retinal ganglion cell growth and differentiation after optic nerve injury.94 Other compounds in research that may alter the cellular apoptosis pathway include neurotrophins, caspasases, epigallocatechin gallate (found in tea leaves), apolipoprotein E, calpain inhibitors, erythropoietin, and autoantibodies against retinal antigens (rhodopsin, glutathione S-transferase, and proteoglycans).94

**Supplements**

Ginkgo biloba, a natural plant compound found in Korea, Japan, and China, has been found to slow VF progression (lower mean deviation and correct pattern standard deviation) as compared with controls, without affecting the IOP, blood pressure, or heart rates. The compound is also useful for the treatment of Raynaud disease, dementia, and cognitive function impairment. The recommended dose for NPG treatment is 120 mg daily. It is postulated that Ginkgo improves VF function by enhancing cerebral and ocular blood flow, retinal sensitivity, and mental concentration. Patients should be cautioned about the risk of bleeding and seizure disorders.91

Resveratrol is a supplement with high antioxidant properties that can be found in the skin of red grapes, peanuts, certain berries, and red wine. It is believed to be vasoprotective by inhibiting endothelin-1 synthesis.95 It is also best known for the cardioprotective, antidiabetic, and anticancerous effects. It increases retinal blood flow to the brain and hence optic nerve. The usual supplement dose is 10 to 200 mg/day but the exact dosing for NPG and its long-term safety and efficacy remain unknown. Other antioxidants like creatine, α-lipoic acid, and nicotinamide are other supplements that have been suggested to have potential use in preventing retinal ganglion cell death.91

**CONCLUSIONS**

NPG falls within the spectrum of OAG but is characterized by more central VF defects, more prominent optic disc cupping, and a higher incidence of disc hemorrhage. It is caused by a large TLCPD causing damage to the optic nerve despite a normal range IOP. OCT is more commonly used to detect preparameiotic disease and systemic associations must be considered when diagnosing NPG. The prevalence of NPG varies among different ethnic populations with highest among Japanese ethnicity and lower in white populations, but it may be underdiagnosed in clinical settings. Current data suggest that NPG may share a large proportion of genetic components of POAG, including both disease-causing (eg, MYOC and OPTN) and susceptibility genes (eg, genes identified in GWASs). Further studies are desirable to identify genes and variants that are specifically implicated in NPG, in which optic nerve damage occurs under normal IOP. Treatment of NPG is multidirectional including control of IOP (with medication, laser trabeculoplasty or surgery), neuroprotection, and improving ocular perfusion via supplements or control of systemic risk factors. Newer compounds targeted at saving or regenerating retinal ganglion cells are being researched. As with any glaucoma subtype, early diagnosis, better patient awareness, regular structural and functional disease assessment, and compliance to comprehensive treatments are best approaches to minimize the impact of NPG.

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