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Research Article

Normal Tension Glaucoma (NTG) - A Probationers Perspective

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Abstract

Normal Tension Glaucoma (NTG) is a common type of glaucoma in which the intraocular pressure (IOP) remains normal despite glaucomatous alterations in the optic nerve, optic disc, and visual field loss, and in which age and ethnicity are important factors in diagnosis. The search was conducted using a variety of online database platforms, with recent authentic articles being considered. The goal of this study is to outline every possible aspect of NTG, including pathophysiology, risk factors that contribute to illness progression, research techniques, and differential diagnosis that aids in early detection and treatment. Systemic vascular anomalies that reach the microvascular level at the location where the optic nerve departs for the visual centers in the brain are the most common cause and contributing factors. Because there are various non-glaucomatous neuropathies that can mimic NTG, a physical examination of the optic disc and its morphology is important in order to rule out NTG in terms of clinical inquiry. Treatment and management, such as preventive IOP lowering therapy, visual field testing, and diurnal variation modulation, can halt disease progression in NTG even at an early stage.

Keywords: Normal Tension Glaucoma; Intraocular Pressure; Primary Open Angle Glaucoma; Optic Disc

Introduction

Glaucoma is a neurodegenerative, irreversible, and usually slow-progressive eye disorder in which there is loss of retinal nerve fibre layer or neural cells with cupping of the optic disc and increased IOP, which is mostly seen bilaterally. NTG, aka low-tension glaucoma, is one of them in which there is normal IOP within the eye but significant and typical changes in the optic disc and visual field defects are seen, which constitutes optic neuropathy [1-3]. NTG is different from POAG as it is caused by various disorders and is commonly independent of IOP as a risk factor [4]. In POAG, when the IOP is within the normal range, it is sometimes called "normal tension glaucoma", as the anterior chamber angle (iridocorneal angle) is open and normal in appearance [5]. Glaucoma, in its early stages, is like a silent thief, robbing vision without the patient's knowledge and emerging as a sight-threatening disease until a late stage is reached, eventually leading to irreversible visual impairment [6]. In glaucoma, the most common risk factor for all clinicians is raised intraocular pressure for optic neuropathy, but in NTG the IOP is normal in range. I.e., IOP<21 mm Hg, the direct clue to glaucoma is not always straightforward. The anterior chamber is quite deep, which makes it overall difficult to predict [7]. Studies suggest that mutations in the glaucoma-causing gene TANK Binding Kinase1 (TBK1) show the typical features of NTG and are a primary cause of the disease, which is also associated with visual field and optic nerve damage [8]. It is important to diagnose glaucoma both structurally and functionally with an optic nerve head examination and a visual field test, respectively [9]. In NTG there are alterations seen in axons, the retinal ganglion cells are comparatively normal all these changes are caused due to ischemia [10]. Early detection of glaucoma can curb the progression of visual field loss by lowering

intraocular pressure or by allocating anti-glaucoma medications. It has been found that small, localised deterioration occurs for almost 5 years in NTG patients [6,11]. This review provides an overview of the current studies and research articles comprising the epidemiology of the disease, pathology or etiology, risk factors, investigation methods, differential diagnosis, and treatment of NTG that make it more interesting, difficult, and different to identify from other glaucomatous optic neuropathy.

Materials and Methods

The study consists of basic aspects and the different articles published. The search for articles was done using online search engines like PubMed, Google Scholar, etc. The search strategy was based on the use of terms in free language related to NTG. The strategies that were used while searching were

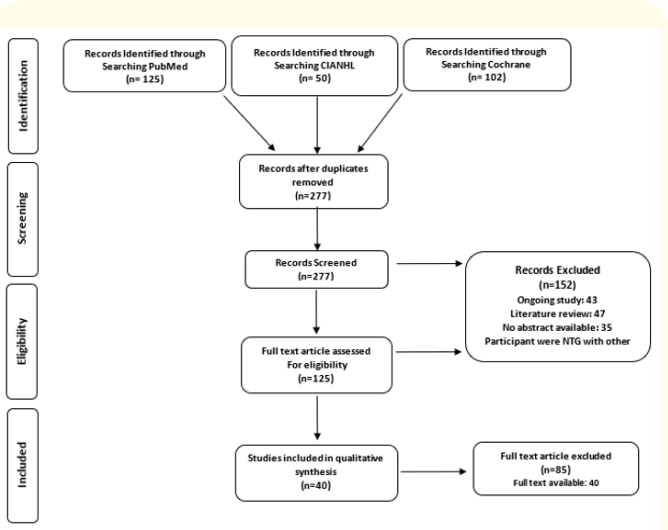

Figure a

Epidemiology

However, the rate of proportion is lacking in our country, especially of NTG cases. There are a few articles which state the proportion and epidemiology of the disease. Previous studies have reported that the Asian population (76.3%) consists of a larger proportion of NTG cases than the white population (33.7%). NTG predominates in the Asian population, with 70% of POAG cases in countries like China, South Korea, Japan, India, and Singapore. The percentage of NTG constitutes the majority of POAG, which is reported in Japan in the Tajimi Study (92%), North China in the Handan Eye Study (83.6%), Singapore in the Singapore Malay Eye Studies (84.6%), Urban South India in the Chennai Glaucoma Study (82%), South China in the Liwan Eye Study (79.3%), and South Korea in the Namil Study (77%). The highest proportion of NTG is in the Tajimi Study and in the Handan Eye Study. The studies in which the white population constitutes less than half of the NTG out of POAG are 38.9% in the Rotterdam Study from the Netherlands, 31.7% in the Beaver Dam Eye Study from the United States of America, and 30% in the Egna-Neumarkt Study from Italy, and the African population constitutes 57.1% in the study from South Africa. The high proportion of NTG in the Asian population has contributed to the proportion of high myopia in Asian countries [12-18].

Etiology

The most common systemic vascular disorders in association with primary vascular abnormalities, which are cardio-vascular abnormalities that lead to decreased optic perfusion or chronic low vascular perfusion, migraine, systemic hypotension, over-treated hypertension, Raynaud's phenomenon, head injury, increased frequency of headaches, obstructive sleep apnea, and other neurological abnormalities have been closely related to insufficient blood supply to the optic nerve in NTG [1,19,20]. There is a proportion of acquired pits of the optic nerve (APONs) in NTG. This structure is due to the loss of neural rim tissue and the lamina cribrosa in the optic nerve [2]. Age and glaucoma have a strong relationship between them in patients who have normal IOP and a suspicious optic disc. It has been reported that Japanese people have the most common form of glaucoma, which is NTG [21]. The vascular factors are mainly involved in NTG and the abnormal blood flow mechanism that leads to its development [22]. Another factor which is responsible for its pathogenesis is high Translaminar pressure difference (TLPD) due to abnormal dynamics of cerebrospinal fluid that induce structural changes by damaging axons and capillaries in the Lamina cribrosa (LC). LC forms a barrier between intraocular space and subarachnoid space, which itself is composed of unmyelinated retinal ganglion cell axons and a thin layer of collagenous tissue. The TLPD is the difference between the IOP and the intracranial pressure (ICP). When the IOP is normal and the ICP is lower, then the TLPD increases accordingly, which leads to optic neuropathy. It has been found in previous

studies that 70% of NTG cases have less ICP, which suggests a positive correlation between TLPD and visual field loss. In NTG patients, higher TLPD leads to a reduction of neuroretinal rim area, which suggests a negative correlation between them [5,12,23]. In Flammer Syndrome, the patient has less ICP, which leads to a raised pressure difference at LC, which results in a decrease in perfusion of the optic nerve. Flammer syndrome affects females more than males. Those patients that display other symptoms of Flammer syndrome such as low blood pressure, reduced feeling of thirst, increased sensitivity to certain drugs, odor, pain, cold extremities, and prolonged sleep onset time also show signs of decreased autoregulation of ocular blood flow, retinal vasodilation reduction after stimulation with flickering light is often associated with NTG [14]. In NTG, IOP also plays an important role in the pathogenesis of the disease. That's why IOP-lowering treatment is very effective in the progression of the disease [13]. Various studies state that primary vascular dysregulation, increased TLPD, mechanical factors, raised sensitivity to IOP alterations, structural thinning at LC, APONs, and peripapillary atrophy at the beta zone altogether constitute the pathophysiology of NTG [1,2,5,6,8,9,12-14,19-26].

Risk factors

The increased risk factors are female gender, myopia or long axial length, obesity, smoking, old age, smaller optic discs, larger vertical cup-to-disc ratio, and impaired glucose tolerance. IOP is also a risk factor for NTG. The Collaborative Normal Tension Glaucoma (CNTG) study suggests that a 30% reduction in baseline intraocular pressure leads to a reduced risk of disease progression. Optic disc haemorrhage is commonly found in eyes with NTG due to microvascular disruption seen in the lamina cribrosa, and optic disc rotation is a risk factor for the progression of the visual field (VF) in the patient's eye. Apart from lowering the IOP, the significant tilt ratio showed greater VF progression. It has been found that there's a relationship between the defects in lamina cribrosa and the vertical tilting of the optic disc [1,21,24]. Inferior disc haemorrhage is seen with the rim notch adjacent to the haemorrhage within the neuroretinal rim and extending to the margin of the disc. The eyes with disc haemorrhage had IOP within the normal range, so disc haemorrhages are independent of IOP [20]. The greater the optic disc tilt or torsion, the greater is the lamina cribrosa defects in NTG patients. The development of lamina cribrosa defects can be due to disc torsion and can together contribute as a risk factor for glaucomatous VF progression. As the axial elongation of the globe produces scleral deformation in increasing myopia, glaucomatous defects and progression become more common in myopic eyes as compared to emmetropic and hyperopic patients [27]. High myopes in the NTG group showed small and tilted optic discs and lower RNFL defects were also seen [28]. The torsion of the disc in the inferotemporal direction and the degree of tilt were associated with the development of NTG in NTG suspects. The lamina cribrosa is found to be thinner in NTG, which contributes less support to blood capillaries and to the nerves in the laminar region, making it more susceptible to damage as compared to POAG. This mechanical rupture of tiny blood vessels can lead to haemorrhages at the level of the lamina cribrosa [19,26]. The most prominent association of NTG is greater optic nerve head (ONH) torsion or tilt when compared to POAG [29]. It has been proven that the presence of optic disc haemorrhage and greater fluctuations of diurnal IOP or diurnal diastolic blood pressure is a confirmed risk factor for glaucoma progression in low-teens NTG eyes. Low-teens IOP is a mean IOP taken after every two-hour interval, and a total of six measurements are recorded. Optic disc cupping and diastolic pressure are associated with visual field defects in NTG [30,31]. The large fluctuations of mean ocular perfusion pressure (OPP), which is calculated as two-third (mean arterial pressure – IOP), is a risk factor for the development of NTG. It has a high correlation with VF loss and disease progression. The OPP is calculated as the difference between arterial blood pressure (ABP) and IOP [12,13]. The authors state that the placement of a ventriculoperitoneal shunt, which is the common treatment for Normal Pressure Hydrocephalus (NPH) treats by lowering ICP, which becomes a potent risk factor for NTG development and further disease progression [15].

Tools for investigation

It starts with the history taking of the patient and includes Goldmann applanation tonometer, gonioscopy, visual field testing, disc angiography, optical coherence tomography, and retinal nerve fibre layer (RNFL) evaluation [1]. The evaluation of the optic disc is the most important part of the assessment [27]. The weak corneal biomechanics due to ageing or various corneal pathologies estimates the IOP less than the actual pressure and states the IOP in a normal range and can delay the treatment, which has to get started until there is permanent and irreversible loss of vision.

In NTG patients, the progression and damage to the visual field is closely associated with corneal biomechanics. For that evaluation of corneal hysteresis (CH) and corneal resistance factor (CRF). i.e., CH-CRF evaluation with the help of ocular response analyzer (ORA) is a powerful tool for the diagnosis of NTG, which is independent of central corneal thickness and IOP. ORA is a more powerful tool for the prediction of NTG progression than central corneal thickness. It helps to record the response to topical medications as well. The CH finding suggests the progression of NTG. The lower the CH value, more is a risk for development of glaucoma especially in elderly patient and Asian population [6,32]. When comparing the glaucoma progression studies, these factors should be considered: ethnicity, disease severity, clinical diagnosis, and disease subtype.33 For morphological characteristics of the optic disc, the Heidelberg retinal tomograph II (HRT II) is a valuable tool for assessment [34].

Differential diagnosis

As there are many other optic nerve related pathologies, there are chances of misdiagnosis in cases in which the IOP is within the normal range and shows glaucomatous changes in the optic disc. It becomes quite challenging and creates a need to differentiate between glaucomatous and non-glaucomatous optic neuropathies, which can mimic each other and can lead to completely different treatment options for eye care professionals. For proper diagnosis and management, it is necessary to evaluate the optic disc and its morphology [25,27]. The most common conditions in which the funduscopic appearance resembles glaucomatous optic neuropathy are ischemic optic neuropathy, compressive optic neuropathy, and congenital abnormalities. They mimic and lead to inadequate treatment and management, which could influence the prognosis of the patient. There are many other differential diagnoses, which are POAG, anterior ischemic optic neuropathy (AION), demyelinating optic neuritis, steroid induced glaucoma, and hereditary optic neuropathy. The most common non glaucomatous neuropathy disease that mimics is arteritic anterior ischaemic optic neuropathy (AAION) and hereditary optic neuropathies [7,35]. The lamina cribrosa is deeper and posteriorly curved in NTG patients than in autosomal-dominant optic atrophy (ADOA), which helps in differential diagnosis and makes LC morphology of utmost importance [36]. Leber hereditary optic neuropathy (LHON) can be misdiagnosed as NTG because there comes a stage in which the optic disc at the atrophic stage of LHON shows the same characteristics like morphological changes and an enlarged cup to disc ratio [35].

Treatment

The first line of treatment for any glaucoma condition is to lower the IOP. The same applies to NTG, which is to lower the IOP in order to prevent or slow down disease progression [1,19,24]. In terms of effectiveness, prostaglandin analogues are the standard treatment for diurnal IOP fluctuations in humans [19,37]. Certain drugs that must be avoided are beta-blockers and adrenergic drugs, which can lead to nocturnal systemic hypotension and optic nerve hypoperfusion. IOP lowering agents are used, such as dorzolamide-timolol fixed combination (DTFC), betaxolol eye drops, nilvadipine, calcium channel blockers like nifedipine, which help in increasing blood flow to the optic nerve head [1]. The detection of disc haemorrhage is important in patients with NTG, but commonly used imaging devices are not capable of detecting such changes, so it intensifies the role of clinical examination by the clinician as 80% of eyes with optic disc haemorrhage have visual field abnormalities, mostly affecting the superior field [20]. Usually, NTG has a slow progression rate in myopic eyes even without giving any IOP-lowering therapy. For further prediction of glaucoma progression in untreated NTG patients with myopia, clinicians must consider age and morphology of the optic disc [38]. During long-term follow-up, it has been found that glaucoma progression is greater in temporally tilted discs in NTG patients than in non-tilted discs [39]. There is no evidence of glaucoma progression due to short-term or long-term IOP fluctuations [40].

Conclusion

In a growing world, the proportion of NTG cases is gradually increasing. In fact, the incidence of cases is increasing faster than the proportion. Early detection and managing the patient with appropriate treatment and further management as NTG is usually asymptomatic until a late or advanced stage is achieved. The advancement of the condition needs more awareness and knowledge among clinicians, optometrists, and ophthalmologists to monitor the progression of the disease. More rigorous studies and investigations are required, which must be followed by a detailed comprehensive clinical examination with frequent follow-up, particularly in older age groups that need specific surveillance by screening and diagnosis in the Asian population.

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Conflict of Interest

The author declares that there are no conflicts of interest in this work.

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Ethics Approval

All procedures performed in the study were following the ethical standards of the Institutional ethics committee and with the 1964 Helsinki declaration and its later amendments.

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