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Normal-Tension (Low-Tension) Glaucoma

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1. Introduction

Normal-tension glaucoma, also known as low-tension glaucoma, is defined as glaucomatous damage to the optic nerve and visual fields with normal diurnal values of intraocular pressure (IOP). The term 'low-tension glaucoma' is not often used because in most patients with normal-tension glaucoma, the IOP is within the higher range of normal values and rarely low. The diagnosis is insidious in many cases and requires a complete and thorough work-up to exclude other causes for optic disc and visual field abnormalities. The definition is problematic because the normal limits of IOP have a wide Gaussian curve range and their effect on the development of glaucoma varies. Some patients may retain a high IOP for many years without any glaucomatous damage, while others with low values of IOP may suffer from ongoing progressive glaucomatous disease. IOP is considered as a risk factor for the advancement of glaucoma even in patients with normal values of IOP, and lowering the IOP often protects the optic nerves (Collaborative Normal Tension Glaucoma Study Group [CNTGSG], 1998). Some optic nerves are more vulnerable even to low levels of IOP than others (Drance et al, 1973). Though many factors have been suspected and investigated, it appears that in addition to variability of the structure of the lamina cribrosa, vascular and genetic factors are most likely involved. Most authors consider normal-tension glaucoma to be a variant of primary open angle glaucoma (POAG) (Caprioli & Spaeth, 1984; Chumbley & Brubaker, 1976); others rely on characteristic clinical features of many normal-tension glaucoma patients to consider it a distinct entity (Caprioli & Spaeth, 1984; Shields, 2008). The debate is ongoing and will probably continue to be the subject of research for many years.

2. Pathogenic theories

The optic nerve damage in normal-tension glaucoma, as in POAG, follows a cascade of pathophysiological events that includes impaired axonal transport, ischemia and free radical formation that leads to apoptosis (Harris et al., 2005). The mechanical theory is based on the assumption that high IOP reduces the axoplasmic axonal flow by causing direct pressure on the axons, resulting in damage to the nerves. Structural differences in the appearance of the optic nerve discs and elastin fibers in glaucoma patients also support the mechanical theory (Dandona et al., 1990; Quigley et al., 1994). The pressure gradient over the optic disc should also be considered, as chronic low intra-cranial pressure may result in a pressure difference that can affect the axoplasmic outflow and lead to glaucomatous progression in normal-tension glaucoma patients.

On the other hand, the vascular ischemic theory suggests that low perfusion to the optic nerve is a major factor in the process of glaucomatous damage. This is supported by many articles that emphasize the importance of low ocular perfusion pressure and blood pressure in the development of POAG (Caprioli & Coleman, 2010). Blood supply to the optic nerve is derived through the ophthalmic artery mainly through the pial system and posterior ciliary arteries, but also from the central retinal artery. Several methods have been used to evaluate the blood flow and resistance of the ophthalmic artery and choroidal vessels, and their relationship with glaucomatous disease progression in POAG and in normal-tension glaucoma patients. Ultrasound Doppler has been used to show correlation between low blood flow and high resistance of the ophthalmic artery, to visual field progression in POAG patients (Galassi et al., 2003). Scanning laser ophthalmoscope demonstrated larger fluorescein filling defects, correlated with low blood flow in the central retinal artery and choroidal vessels of normal-tension glaucoma patients compared with controls (Plange et al., 2003). Heidelberg retinal flowmetry has detected a reduction in neuroretinal rim blood flow in conjunction with visual field defects in normal-tension glaucoma patients (Sato et al., 2006). The future of understanding the ischemic aspect in the development of glaucoma may be by optical measurement of retinal vessel oxygenation. Oxygenation of retinal arteries was found to be lower in normal-tension glaucoma patients than in healthy subjects (Michelson et al., 2006). Other factors influence the perfusion of the optic nerve and participate in the development and progression of the disease. Hypertension leads to a greater resistance in small blood vessels and causes atherosclerotic changes. Hypotension, especially in the presence of insufficient vascular autoregulation, may participate in the development of the ischemia (Goldberg et al., 1981). Circadian fluctuation of mean ocular perfusion pressure was found to be an important clinical risk factor for severity of glaucoma in eyes with normal-tension glaucoma (Choi et al., 2007). Nocturnal dips have also been evaluated and are thought to play a role in the development of normal-tension glaucoma (Bechetouille et al., 1995; Graham et al., 1995). Another observation that indirectly supports the vascular theory is that many normal-tension glaucoma patients suffer from vasospastic diseases such as migraine (Corbett et al., 1985; Phelps & Corbett, 1985) and Raynaud disease (Broadway & Drance, 1998). However, other studies found no difference in the prevalence of atherosclerotic vascular disease in NTG and POAG patients (Klein et al., 1993; Leighton & Phillips, 1972). The role of vascular disease in the pathogenesis of NTG is probably related to the reduction of optic nerve resistance to the IOP and this may precedes changes in vasculature that occur also in POAG. Many believe that both theories have a part in the pathogenesis and their importance in the advancement of the disease varies from patient to patient.

3. Epidemiology

Normal tension glaucoma has been found to be common in many population-based studies, though the numbers vary in different studies and populations. The main reasons for the variation are the difference in normal IOP range in different populations and the difficulty in making the diagnosis. Ruling out high-tension glaucoma by diurnal measurements was not performed in most of these studies. Other causes of "burned out" secondary glaucoma such as steroid-induced or uveitis-related glaucoma were not diagnosed and excluded in some studies. Large epidemiological studies in North America, Europe and Australia estimated the prevalence of normal-tension glaucoma to be up to half that of POAG (Leibowitz et al., 1980; Sommer et al., 1991). The Beaver Dam Eye Study estimated the prevalence of normal-tension glaucoma to be up to 1.6% in patients over 75 years of age

(Klein et al., 1992). In Japan the prevalence is considerably higher. The Tajimi eye study assessed the prevalence of POAG in patients over 40 years and found it to be 3.9%, in 92% the IOP was 21 mmHg or lower (Iwase et al., 2004). A nationwide survey estimated the normal-tension glaucoma with (IOP under 21mmHg) prevalence to be 3.5 times that of POAG, but these numbers are thought to be biased since normal IOP in Japan is lower than in the western population, averaging 10-18 mmHg. The prevalence of normal tension glaucoma is higher in women than in men, this and other risk factors will be discussed later in this chapter. Whatever the prevalence of normal tension glaucoma is in various populations, it is obvious that the numbers are higher than once assumed, and patients are actually diagnosed only when optic disc and visual field abnormalities are already present.

4. Genetic considerations

Family history is a major risk factor in glaucoma, and genetic mutations related to specific phenotypes of glaucoma are under investigation. Such information can help diagnose and classify subtypes of glaucoma, and perhaps even to clarify the pathogenesis. Research may find ways to repair mutation in utero or early in life, before glaucomatous damage has occurred. Genetic research has found transmission of a NTG phenotype in only a few families, all of them are autosomal dominant (Bennett et al., 1989). Of the seven gene loci that have been linked to POAG, two genes have been identified and named TIGR/ Myocilin and Optineurin (Optic Neuropathy-Inducing Protein - ONTP). A specific mutation GLC1E locus of the ONTP was found in location 10p14-15, with autosomal dominant inheritance as in all POAG loci that were identified (Sarfarazi et al., 1998). ONTP is expressed in the retina and was found to be involved in apoptosis. The Blue Mountains Eye Study in Australia found that the prevalence of mutation in the ONTP gene was higher in POAG than in healthy subjects but the difference was not statistically significant (Baird et al., 2004). Reports found the ONTP mutation associated with high prevalence of POAG and NTG in adult Japanese patients, suggesting it may be involved in the pathogenesis of both entities (Fuse et al., 2004; Umeda et al., 2004). Other reports could not find OPTN mutations in NTG (Toda et al., 2004). Genetic screening for the gene is not an option because of the low incidence of the mutation. Recently another locus GLCA3 was investigated for association with NTG, but no statistically significant relationship was found (Kamio et al., 2009).

5. Diagnosis and differential diagnosis

The diagnosis of normal-tension glaucoma is illusive and requires a high degree of suspicion. Since IOP measurements are usually in the high teens in normal-tension glaucoma, routine IOP screening measurement may be deceiving. Often, the first sign is an abnormal optic disc or disk asymmetry suspicious of glaucomatous damage. In up to half of the patients repeated measurements or daily IOP curve discovers high IOP, and the diagnosis of POAG is made (Ito et al., 1991; Perkins, 1973). The significance of a daily IOP curve in the diagnosis of NTG is crucial. Few other factors must be considered. Pachymetry should be performed to adjust the difference between measured IOP by Goldman tonometry and true IOP. Ocular hypertension study (OHTS) highlighted the importance of thin corneas in the diagnosis of glaucoma. Thinner corneas can lead to underestimation of IOP, and misdiagnosis has occurred in many NTG patients compared with POAG patients (Morad et al., 1998). The effect of corneal hysteresis and scleral rigidity should be considered and Ocular Response Analyzer (ORA) can help in estimating the true IOP (Morita et al.,

2010). Thin corneas following corneal refractive surgery and in patients after penetrating or lamellar keratoplasty can make the task of IOP estimation more challenging (Papastergiou et al., 2010; Sanchez-Naves et al., 2008). Other factors such as refraction and astigmatism should also be considered and ORA may achieve a better estimation of the true IOP in these patients (Hagishima et al., 2010).

The controversy of whether NTG is different from POAG is demonstrated in many articles regarding optic disc appearance. While some studies show no difference in the optic disc appearance between NTG and POAG (Tomita, 2000), others found distinct characteristics such as thin rim that can help distinguish NTG (Caprioli & Spaeth, 1985). OCT plays a major role in the diagnosis and monitoring of glaucoma especially when the diagnosis is not certain. Measuring the RNFL thickness, optic disk cupping and their correlation with visual field abnormalities is a powerful tool. Recently a study comparing the optic discs using optical coherence tomography (OCT) and Heidelberg retina topography (HRT) supports some of the differences (Shin et al., 2008). Disc appearance in NTG is traditionally divided into two sub-groups. The more common is the senile sclerotic group, which is characterized by a pale shallow sloping neuroretinal rim. These patients are often older in age and suffer from vascular diseases. The other group, focal ischemic, is characterized by deep focal notching of the rim. Splinter hemorrhages are a typical finding in NTG and imply in most cases a progressive disease (Drance et al., 2001; Jonas & Xu, 1994). Beta zone peripapillary atrophy has also been suggested related to optic nerve damage in NTG (Xia et al., 2005). The site of the hemorrhage may predict an area of notch development with a correlated visual field loss (Chumbley & Brubaker, 1976; Siegner & Netland, 1996; Tomita, 2000). Visual field patterns in NTG are similar to the ones seen in POAG, still some articles found differences in the distribution and shape of the scotomas. Scotomas observed in NTG visual fields often tend to be deeper, steeper and closer to fixation than in POAG patients (Caprioli & Spaeth, 1984; Harrington, 1960). Some articles mainly from Japan found that scotomas in NTG may be more predominant in the lower hemifield (Araie, 1995).

The ophthalmologist should rule out "burned out" secondary glaucoma and other misleading diagnosis. Careful history and meticulous ophthalmic examination should look for previous trauma, uveitis, glaucomatocyclitic crisis, pigmentary glaucoma, previous topical or systemic steroid treatment, previous acute angle closure attack and the use of systemic medication that lowers IOP (e.g., beta-blockers). Compliance should be appreciated to rule out the possibility that the patient takes his anti-glaucoma medications only before the ophthalmologist examination in order to "please" their doctor. Non-glaucomatous optic disc abnormalities such as congenital colobomas, optic nerve pit, anterior ischemic optic neuropathy, traumatic optic neuropathy, optic nerve or chiasm compressing lesion, and various retinal abnormalities should be considered and revoked. The diagnosis and follow-up of NTG is more challenging with hypoplastic and myopic tilted discs. Systemic evaluation is advised to identify diseases that are more frequent in NTG patients, and when the diagnosis is difficult. Blood pressure, ischemic vascular disease, perfusion pressure, vasospastic disorders (migraine, Raynaud phenomenon) and obstructive sleep apnea should be assessed in selected cases. Some cases may require neurological evaluation and hematological work-up to search for various neurological conditions or coagulopathies. Generally, systemic evaluation is reserved for atypical cases when the optic disc appearance and visual field do not correlate with glaucomatous damage, when glaucomatous damage is found with IOP lower than the high teens before treatment or when other neurological symptoms are present. Neurological examination is vital in all cases of NTG with atypical

clinical manifestation. Lesions such as meningiomas, craniopharyngiomas, pituitary adenomas, and compressive vascular lesions such as aneurisms can mimic NTG. Some ophthalmic signs are more suggestive of a neurological disease and should prompt a neurological evaluation. Perhaps the most important of them is a rapid progression of the disease despite low IOP with or without treatment. Other signs that should raise suspicion are pale optic disks and poor best corrected visual acuity. Needless to say any neurologic symptoms prompt neurologic workup. Some authors believe that it is important in all cases of NTG to perform a CT scan (Gutman et al., 1993), though others found no value for a routine neurological examination in NTG patients (Kesler et al., 2010).

Risk factors for the development of NTG in untreated patients that were found in the Collaborative Normal Tension Glaucoma Study (CNTGS) are migraine, female gender and splinter disc hemorrhage at the diagnosis (Drance et al., 2001). Age over 60 years is common (Klein et al., 1992), and a high prevalence was found in Japanese as mentioned earlier (Iwase et al., 2004; Shiose et al., 1991). Other risk factors found to be more prevalent in NTG than in POAG patients were ischemic vascular disease, obstructive sleep apnea, autoimmune diseases, and coagulopathies, but their effect on development of NTG was not consistent.

The progression of glaucomatous damage in NTG is usually very slow. Collaborative Normal Tension Glaucoma Study (CNTGS) showed that half of the untreated patients did not progress in 5 years, and in most cases the progression was slow (Anderson, 2003). In some of these patients a previous hypotensive crisis from a massive bleeding or arrhythmia resulted in optic disk cupping. (Drance, 1977). In patients without a subsequent hypotensive crisis the glaucoma is not expected to progress. Other cases such as steroid responders or "burned out" pigmentary or uveitic glaucoma may not progress at all. Despite their effect as risk factors for the development of NTG, neither age nor untreated level of IOP affected the risk for progression in untreated eyes (Anderson, 2003). Disc hemorrhages, as mentioned earlier, were also found to be related to the progression of glaucomatous damage (Ishida et al., 2000).

6. Practical steps for diagnosis

It is difficult to diagnose NTG if the cup to disc ratio is over 0.5 even if the differences in cupping are 0.2 or higher in the presence of normal IOP. At this stage, the visual fields are usually normal. If the cornea is thin, POAG may be suspected after correction of the IOP according to the corneal thickness. But if the corneal thickness is normal, the diagnosis of NTG cannot be established. Those patients may stay with the diagnosis of glaucoma suspects until new signs of disk abnormalities appear that correlate with the glaucomatous visual field defects. Although these patients may deteriorate slowly, other glaucoma patients may deteriorate rather quickly. Therefore, it is recommended to follow individuals over the age of 40, glaucoma suspects and individuals with family history, at least every 6 months. There have been cases where glaucoma appeared and progressed within less than a year, and this is the reason for a 6 months routine follow-up. Preperimetric normal tension glaucoma should be evaluated using FDT or Swap when available.

The diagnosis is made when optic disc cupping and glaucomatous visual field defects are found in conjunction with normal IOP. POAG should be ruled out by corneal pachymetry and adjustment of the IOP to the corneal thickness. Other causes for optic disc cupping and visual field defects should be ruled out by detailed anamnesis (e.g., episodes of major blood loss) and further analysis (e.g., brain computed tomography to rule out tumors as mentioned earlier).

7. Treatment

The decision to treat a patient suspected with NTG must include the patient's age and all aspects of the disease, its extent, pathogenic factors and especially the rate of progression. If the patient's disease seems not to be progressive, monitoring of the disease is advised. When the disease is bilateral and not severe, treatment in one eye may be suitable. Careful follow-up and comparison of both eyes for progression is essential. Some patients suffer from visual field loss and disc damage and require prompt therapy. As in POAG, it is customary to begin with medical therapy, but laser and even surgical treatment should be considered for advanced cases. The target IOP was recommended to be 30% reduction by CNTGS and this reduces the progression from 35% in untreated patients to 12% in the treated group. Approximately two-thirds of the patients that did not receive any therapy did not progress (Drance et al., 2001). Target IOP was reached with medication and laser trabeculoplasty in half of CNTGS patients. This was achieved without beta-blockers or prostaglandin analogs. Currently the available drugs are thought to produce better effects on lowering the IOP, better compliance and better results in preventing disease progression. Still some patients continue to deteriorate after proper IOP reduction.

Some drops especially brimonidine were found to have neuroprotective effects in animal models (Vidal et al., 2010; Wolde Mussie et al., 2001). The research to achieve better control of glaucoma using a mechanism other than lowering IOP is promising. Unfortunately, neuroprotection by preventing the death of retinal ganglion cells, and vision preservation have not yet been proven in humans (Saylor et al., 2009). Long-term follow-up should determine whether or not neuroprotective agents may be beneficial for glaucoma patients (Sena et al., 2010). A low-tension glaucoma study LoGTS is currently underway comparing timolol and brimonidine treatment in NTG patients. The authors believe the neuroprotective effect of brimonidine will provide better results in preventing the disease progression. Dorzolamide, betaxolol, and latanaprost were considered to increase blood flow around the optic nerve (Harris et al., 1996, 2000), but newer published studies suggest that the effect, if exists at all, is minor (Bergstrand et al., 2002; Harris et al., 2003). Calcium channel blockers treatment was proved to be beneficial (Koseki et al., 2008; Netland et al., 1993). The treatment is recommended especially if a vasospastic disorder is diagnosed. Systemic side effects of calcium channel blockers such as flushing, edema, hypotension, headaches and reflex tachycardia requires careful selection of patients for this therapy.

In patients with low compliance or troubling side effects, laser treatment should be considered. Selective laser trabeculoplasty has promising results on lowering IOP and is considered a safe and reproducible treatment for NTG (El Mallah et al., 2010; Realini, 2008). Argon laser trabeculoplasty was studied as treatment for normal-tension glaucoma patients. The results varied from little to no effect (Schulzer, 1992; Sharpe & Simmons, 1985). SLT is considered a safe and effective treatment for lowering IOP, especially in noncompliant patient and in patients with severe side effects from topical or systemic drug treatment.

Trabeculectomy was found to lower IOP and slow the progression after long term follow-up (Bhandari et al., 1997; Shigeeda et al., 2002). Both medical and surgical treatments increase the risk for cataract formation. Cataract development was more frequent in patients undergoing trabeculectomy than in patients receiving only medical treatment (Drance et al., 2001). Follow-up and cataract extraction is advisable to improve visual acuity and follow-up reliability. Finally any systemic disease that can affect optic nerve perfusion such as systemic

hypertension, congestive heart failure, arrhythmia and anemia, should be treated (Chumbley & Brubaker, 1976).

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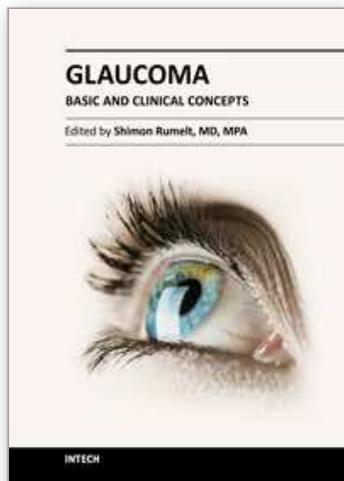
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