Normal tension glaucoma—a practical approach

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Normal tension glaucoma (NTG) remains a difficult diagnosis for the ophthalmologist who favours the argument that raised intraocular pressure (IOP) is essential for the diagnosis of primary open angle glaucoma (POAG). The concept of NTG challenges us to distinguish between pressure dependent and pressure independent causal factors. The purpose of this review is to present some of the current information on the epidemiology, aetiology, and management of NTG, based upon a review of recent literature and experience with more than 400 NTG patients attending the glaucoma service at Moorfields Eye Hospital.

Definition of normal tension glaucoma
It is important to define NTG in order to distinguish it from other forms of glaucoma and to be able to manage it in the most appropriate way. The inclusion of a typical glaucomatous optic neuropathy with characteristic field defects in the defining criteria poses few problems. However, the level at which intraocular pressure (IOP) becomes abnormal has been a source of conjecture in the ophthalmic literature and the pros and cons of setting an arbitrary limit for use in the definition of NTG have been discussed elsewhere. To try and simplify the issue we have included the following criteria for the definition of NTG as used in our clinic at Moorfields:

- A mean IOP off treatment consistently equal to or less than 21 mm Hg on diurnal testing, with no single measurement greater than 24 mm Hg
- Open drainage angles on gonioscopy
- Absence of any secondary cause for a glaucomatous optic neuropathy—for example, a previously raised IOP following trauma, a period of steroid administration, or an episode of uveitis
- Typical optic disc damage with glaucomatous cupping and loss of neuroretinal rim
- Visual field defect compatible with the glaucomatous cupping (disc/field correlation)
- Progression of glaucomatous damage.

The requirement that the disease be progressive is controversial. NTG is usually a progressive disease although this may not be manifest for several years. However, it may not be practical or ethical to wait for progression to be clearly demonstrated before making a diagnosis of NTG. The diagnosis is therefore essentially made on the basis of optic nerve and visual field characteristics along with diurnal IOP measurements. Nevertheless, the progressive nature of the disease should always be borne in mind as this will help to distinguish true NTG from an isolated ischaemic event which may mimic it in terms of optic disc and visual field appearances.

Epidemiology
There are around 150 000 patients in the UK with diagnosed glaucoma and the same number again with undiagnosed disease. One third of the patients with POAG can be classified as having NTG. Bearing in mind that glaucoma is currently the second commonest cause of blindness worldwide, and it is estimated that by the year 2000 it will be the commonest cause of untreated blindness, the prevalence of NTG faces us with a substantial problem. In the UK the majority of new referrals to the glaucoma service are from optometrists performing screening tonometry in the community; hence, many more cases of NTG may be left undiagnosed. However, with the advent of routine ophthalmoscopy and visual field assessment by optometrists the detection rate may be seen to rise in the future.

NTG is a disease of the elderly. In the Beaver Dam Eye Study the prevalence of likely NTG increased from 0.2% in the 43–54 years age group to 1.6% in those over 75 years of age. However, there is a significant minority of patients who are below the age of 50 years, with figures ranging from 11% to 30% of all cases. These patients are perhaps the ones for whom effective management of their disease is the most crucial as their potential life span provides the possibility of more advanced disease as they age. In Japan the prevalence of NTG is probably higher than in the West because of the tendency there for IOP to fall with increasing age. It has been reported that four times as many patients in the over 40 age group have NTG as have high tension glaucoma (HTG), accounting for 2% of the Japanese population.

It has been suggested that NTG is more prevalent in the female population. Levene’s review of the relevant studies found an overall higher female prevalence ranging from 6% to 75%. The Beaver Dam Eye Study found equal prevalence among the sexes. There is a preponderance of females in the Moorfields NTG group with a ratio of 2:1 in all age groups. This potential sex difference is important because there is evidence that the disease may have a worse prognosis in females and because of the clues it gives of possible pathogenetic factors.

There appears to be a genetic component to the development of NTG. Several cases of both NTG and HTG may occur in the same family. The presence of a positive family history has been reported in 5% to 40%. Relatives of affected patients should therefore attend for case finding by an optometrist.

Aetiological factors
Factors involved in the aetiology of glaucomatous optic neuropathy can be divided into pressure dependent and pressure independent groups, and these are discussed further, in relation to NTG.

Pressure independent causes
These may be subdivided into (1) abnormal blood flow, (2) systemic hypotension, (3) abnormal blood coagulability, and (4) other factors.

Much current interest in NTG has focused on the possibility of reduced flow in the blood vessels supplying...
the optic nerve head. Blood flow in these vessels depends on various factors including blood pressure, IOP, vascular resistance, and autoregulatory mechanisms. The viscosity and coagulability of the blood constituents may also have an effect on tissue perfusion. The importance of considering these factors is whether they provide us with any therapeutic options for NTG.

Role of abnormal blood flow
Optic nerve blood vessel diameter may be affected by vasospasm and the association between vasospastic disorders and NTG may give us some clues to mechanisms of damage. Convincing associations have so far been drawn with migraine headache and Raynaud’s phenomenon. Drance, Hitchings et al found decreased finger capillary flow in NTG patients suggesting vasospasm as an underlying aetiological factor. Another study using colour Doppler imaging found increased resistance in the ophthalmic and central retinal artery in NTG patients compared with controls.

Several studies have investigated the effect of reversing vasospasm by different mechanisms. It has been postulated that this vasospasm may be reversible with calcium channel blockers, which leads to relaxation of the vessel walls. Kitazawa et al found that after treatment with the calcium antagonist nifedipine for 6 months, a small proportion of patients showed an improvement in visual fields. Caution should be exercised in interpreting these results owing to long term fluctuation in visual fields over time. Netland et al retrospectively looked at NTG and HTG patients who were on calcium channel blockers for medical reasons and found in the NTG group that patients on these drugs were less likely to progress. One limitation of this approach is that the different patient groups were not matched for systemic vascular status. Another study from Japan prospectively followed 28 NTG patients assigned to either treatment with the calcium antagonist brivancamine, or with a placebo. The brivancamine treated group showed a relative improvement in the visual fields using STATPAC 2 over a mean follow up period of 38 months. Flammer concluded in his review on calcium channel blockers that calcium antagonist nifedipine has a role in the treatment of some NTG patients in whom there is some evidence of a vasospastic syndrome (as assessed by nail fold capillaroscopy) and in whom a short course trial has improved or stabilised the visual field. Topical betaxolol may have a calcium antagonist action and its effect on ocular blood flow has been investigated by preliminary studies on groups of HTG patients. Drance et al found decreased blood flow in NTG and also increased red capillary flow in NTG patients suggesting vasospasm as an underlying aetiological factor. Another study using colour Doppler imaging found increased resistance in the ophthalmic and central retinal artery in NTG patients compared with controls.

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These studies suggest that nocturnal dips should be looked for in all NTG patients using oral hypotensives, and if present this should be modified accordingly.

Contribution of an abnormal coagulability profile
The contribution of an abnormal coagulability profile to glaucomatous damage has been investigated by several groups. Drance 12 found a relatively hypercoagulable state but this was not confirmed by subsequent publications. Weinreb 39 could not draw any firm conclusions in his review of the subject, but did suggest that future studies into abnormal rheology should involve untreated glaucoma patients as the effect of medication on blood constituents is unknown. A recent study by O’Brien et al 39 found a relative activation of the coagulation cascade and fibrinolysis pathways in POAG and NTG compared with controls, although this finding was more significant in the POAG group. Hamard et al 39 using a laser Doppler velocimeter found decreased blood flow in NTG and also increased red cell aggregability. It can be concluded that although as yet there is no consistent evidence as to the presence of an abnormal rheology in NTG, the presence of abnormalities should be considered with each NTG patient.

Other factors
Drance 12 found that a history of hypotensive shock, or episode of severe blood loss was more common in NTG patients and a full history should be taken with questions relevant to this point. Goldberg et al 39 found that NTG patients had a higher incidence of cardiovascular disease and a sedentary lifestyle than a group of ocular hypertensive controls. Other groups have not confirmed these findings.

An association between ischaemic changes in the brain and in the optic nerve reflecting a common aetiology has been investigated. Ong et al 39 found a higher incidence of cerebral infarcts on magnetic resonance imaging (MRI) in a group of NTG patients compared with age matched controls. Another group using computed tomography (CT) found no such difference, although this method of neuroimaging is less likely to pick up asymptomatic lesions. The association between NTG and carotid artery disease has been investigated without any clear conclusions. There is no real evidence as yet that NTG patients have more carotid disease than the normal age matched population. In conclusion, it is likely that abnormal
blood flow affecting the optic nerve can contribute to the optic neuropathy of NTG. The preceding studies have suggested possible therapeutic options which may increase optic nerve head blood flow such as calcium channel blockers, betaxolol drops, and modification of antihypertensive treatment. Evidence to support the use of calcium antagonists in the treatment of NTG is promising, but more long term prospective studies are required to assess more precisely the risks and benefits of such therapy.

ROLE OF IOP

Although the IOP in NTG lies within the normal range, there is still suggestive evidence that it is a “risk factor” for the development and progression of the disease and that one therapeutic option is to lower IOP to “low normal” levels. Several studies have suggested that intereye differences in IOP do occur in patients with NTG. Cartwright and Anderson\(^15\) looked at 14 cases of NTG with asymmetric IOP and found that in 12 cases the extent of glaucomatous cupping and visual field loss was greater in the eye with the higher pressure. This study was limited by being retrospective, and included only small numbers of cases. The degree of asymmetry found ranged from only 1–5 mm Hg, and the study was not controlled for the length of time from initial diagnosis to review of the fields and disc photographs. Crichton et al.\(^43\) also found that in the presence of unequal IOP, the visual field damage was greater on the side with the higher mean IOP, but that only 28% of patients with asymmetric fields had IOP asymmetry of \(\pm 1\) mm Hg. Haelliger and Hitchings\(^44\) found no relation between the higher IOP and the more severe field loss in 78% of 60 untreated NTG patients, with the remaining 22% showing some correlation. They postulated that there may indeed be two distinct groups in which pressure may or may not have an influence on disease outcome. Arai et al.\(^45\) retrospectively evaluated the contribution of several factors on visual field progression in 56 eyes and found that the IOP level had a significant influence. Conversely, in his earlier review Levene\(^9\) concluded that overall there was no influence of IOP. Other studies have examined the aetiological role of IOP in NTG indirectly by determining whether lowering the IOP effectively alters the rate of progression. Abedin et al.\(^46\) found in a case report series that lowering the IOP to a value less than 12 mm Hg by surgery arrested the progression of visual field loss and optic disc cupping in a group of NTG patients. De Jong et al.\(^47\) found that an average reduction from 18 mm Hg to 10 mm Hg led to a significant slowing of progressive visual field loss. Yamamoto et al.\(^48\) carried out a prospective investigation of the postoperative IOP level, visual function changes, and postoperative complications of trabeculoplasty with mitomycin C in NTG.\(^49\) In this series of 31 eyes, the mean preoperative IOP was 14.1 (SD 1.9) mm Hg, which was reduced by a mean of 5.8 mm Hg following surgery. Eighty seven per cent of eyes achieved IOPs within the range of 5–12 mm Hg, and this led to a cessation of visual field progression in the majority of eyes. We also looked at the effect of surgery on progressive NTG with a prospective, controlled clinical trial.\(^50\) We followed 18 patients with bilaterally progressing visual fields, who underwent fistulising surgery on one eye only, with the fellow untreated eye acting as a control. On average, a 30% reduction of the IOP was achieved following surgery. Visual field data collected for both the treated and the fellow eye over the 2 years after the date of surgery were analysed, and the untreated eye showed a much larger number of significantly progressing retinal locations and these deteriorated at a faster rate than in the treated eye. A more recent study from our clinic reported by Bhandari et al.\(^51\) confirmed that surgery which achieved on average a 30% reduction in IOP resulted in a slower rate of visual loss than would be expected if the eye was left untreated. These two studies did not use antiproliferatives but it has been suggested that the use of such drugs perioperatively may give a greater and more sustained IOP decrease in these patients.\(^52\)\(^53\)

Other studies which did not find any effect of IOP reduction on the rate of deterioration in NTG did not always achieve the desirable 25–30% reduction in IOP. The Normal Tension Glaucoma Study Group is an ongoing multicentre clinical trial investigating the effect of achieving a 30% reduction in IOP on the rate of progression. An early publication\(^54\) suggested that this degree of IOP lowering could be achieved by methods other than surgery—that is, by drops with or without laser trabeculoplasty (LTP), or by LTP alone. Medical treatment should be used if the IOP reduction can be maintained at 25–30% but this may not always be achieved.\(^55\)\(^56\) However, with the recent introduction of prostaglandin analogues, latanaprost has already been reported on as a potential drug for achieving adequate IOP reduction.\(^57\)

Differences in the clinical characteristics of NTG and HTG have been extensively studied, and it has been suggested that these may reflect differences in the relative contributions of any underlying aetiologies of the two disorders.

Does the pattern of optic disc cupping differ between NTG and HTG?

There has been much debate as to whether optic disc morphology differs between NTG and HTG. If it does, then this may reflect differing contributions from underlying aetiologies such as abnormalities in disc architecture and blood flow characteristics. Tezel's group\(^58\) looked at large numbers of patients with NTG, POAG, and ocular hypertension (OHT) to determine whether there were significant differences in disc morphology between the groups. They found more advanced neuroretinal rim loss in the NTG group with increased peripapillary atrophy but they acknowledged that this was probably due to a relatively late presentation of this group of patients. They also noted a higher incidence of optic disc haemorrhages in NTG than the other groups and this finding has been confirmed by others.\(^59\)\(^60\) The prognostic significance of these haemorrhages in terms of progression has already been well established.\(^61\)

Acquired optic disc pits which are thought to be due to focal loss of neuroretinal rim tissue and shown as localised excavations of the lamina cribrosa, are more frequent in NTG.\(^62\)\(^63\)

Miller and Quigley\(^64\) compared the disc photographs of 25 NTG patients and 26 control patients with HTG and found no differences in shape or size, C/D ratio, or position of rim loss. They did, however, find a difference in the configuration of connective tissue bundles in the lamina cribrosa and speculated that this may represent a structural aetiological factor of the damage occurring with NTG. Tuulonen and Airaksinen\(^65\) found larger discs in NTG compared with POAG and exfoliative glaucoma.

Geijssen and Greve\(^66\) felt that there were three distinct groups of NTG patients according to their optic disc appearance—focal ischaemic, senile sclerotic, and myopic—each with different prognostic and possibly aetiological significance.

Levene concluded in his review that the extent of disc cupping in NTG is often greater than would be expected from the size and depth of the visual field defect present. This finding was backed up by a study carried out by Caprioli and Spaeth\(^67\) who also found more sloping cup
pattern of cupping between NTG and HTG. There is some evidence that the degree of visual field defect in NTG may be related to the amount of peripapillary atrophy present (especially zone beta) and this may be useful in the evaluation of patients. 50

Are the visual field defects different in NTG and HTG?

Levene considered that the frequency of dense defects extending to within 5 degrees of fixation was higher in NTG than HTG. In a perimetric study Hitchings and Anderton 51 found similar results. These studies, however, analysed visual fields obtained using manual perimetry. Caprioli and Spaeth 52 looked at automated Octopus fields and found that scotomas in their low tension group had a steeper slope, were closer to fixation, and were of a greater depth than the HTG group. Chauhan et al. 53 examined field loss using the Humphrey field analyser and found that defects in NTG tended to be more localised than that in HTG, when the extent of field damage and visual acuity were closely matched. Some studies have suggested that differences in the pattern of visual field defects may be age and IOP dependent—for example, with more diffuse defects appearing in younger patients with higher IOPs. 54

Several groups have shown that the superior hemifield is most frequently affected in NTG. 55 56 Fontana et al. 57 retrospectively looked at the frequency and pattern of visual field loss in the “normal eye” of 53 initially unilateral NTG patients over an extended follow up period. They found that 30% of the patients converted to an abnormal visual field over a median period of 25 months. The initial field loss occurred in a paracentral location in 87% of patients and the superior hemifield was the site of conversion in 70%. Interestingly, the topographical distribution of the field loss in the initially affected eye correlated with the site of onset of damage in the initially normal eye in 75% of cases.

Other studies have found no differences in the pattern of visual field loss seen in NTG and HTG. 58 Arsic 59 concluded in his recent review of the relevant literature that when NTG patients are compared with HTG patients with a overall similar extent of field damage, then there is a difference between the two groups, with the NTG field defects being relatively more localised and closer to fixation. However, if they are matched for the degree of optic disc involvement then there are no intergroup differences. It is also possible that presentation of the NTG patient is relatively delayed compared with that of the patient with raised IOP, and may occur only when he becomes symptomatic from a central field defect. This mode of presentation should become less common as time to detect change. Anderton et al. 60 found on the basis of follow up with Goldmann fields that the size of the visual field defect increased in 40% of patients over a 10.5 year period. Gliklich et al. 61 used Octopus automated perimetry to follow a group of treated NTG patients and using clustering analysis techniques found that 53% showed progression at 3 years rising to 62% at 5 years.

Detection of progression

No treatment is required for the NTG patient who is stable. Treatment options should be reserved for those who are progressing, so that unnecessary treatment side effects are avoided. Glaucoma management still relies heavily on the interpretation of sequential visual fields over time to detect change. Anderton et al. 51 found on the basis of follow up with Goldmann fields that the size of the visual field defect increased in 40% of patients over a 10.5 year period. Gliklich et al. 61 used Octopus automated perimetry to follow a group of treated NTG patients and using clustering analysis techniques found that 53% showed progression at 3 years rising to 62% at 5 years. It has been demonstrated that the mode of visual field progression in NTG is linear. 62 The detection of change by the analysis of global visual field indices may be useful if there is considerable noise present in the data, but it may overlook the presence of early more localised changes. Therefore, in order to achieve the goal of accurately identifying and treating those patients that are deteriorating we need a sensitive way of detecting progression, and with the more widespread use of standardised Humphrey perimetry this may be possible using linear regression techniques which examine sensitivity changes at individual stimulus locations. A recent study using pointwise linear regression analysis techniques retrospectively looked at visual fields on 168 eyes and found progressive change in 37% of eyes. However, this was over a mean follow up of only 28 months. Linear regression analysis on a larger group of patients at Moorfields indicates that with an increased follow up time, the figures rise to 50% at 3 years and over 95% at 6 years using similar methods of analysis. In this group, three visual fields per year is practical and allows progression to be identified. In our experience, the rate of change may vary from no detectable change in retinal sensitivity over a period of 10 years or more, to upwards of 5 dB loss at individual retinal points a year. Treatment is appropriate when visual field deterioration is identified and at a rate likely to affect the patient in his or her lifetime. Although sequential visual field analysis currently provides
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**IOP LOWERING TREATMENTS**

As has been noted above, IOP lowering >25% seems necessary to be effective in at least slowing the rate of visual loss in NTG. Although this can be achieved by topical hypotensive medication, at the present time fistulising surgery with the use of an antiproliferative is the treatment most likely to achieve this in the NTG patient with presurgical IOPs at the lower end of the normal scale; however, a 25% + fall in IOP carries a real risk of postoperative hypotony. Because of this complication (which will render a frequently asymptomatic patient very symptomatic) we reserve fistulising surgery for patients with undoubted visual field progression for whom the 25–30% fall in IOP is achievable but for whom medical treatment does not succeed in achieving this aim. In many instances this requires almost immediate surgery as the ability of β blockers to lower the IOP which is already within the normal range is limited. However, some studies have shown that once a day latanaprost may lead to a satisfactory drop in the IOP in NTG.

**NON-IOP LOWERING TREATMENTS**

These include the use of oral calcium antagonists, and topical agents such as betaxolol. Newer agents such as brimonidine which may have a neuroprotective action have yet to be evaluated for use in NTG. These agents need to be considered where an IOP reduction of 25–30% cannot be achieved, or if visual field progression continues despite it.

At Moorfields Eye Hospital we perform 24 hour home BP monitoring on patients who appear to be progressing. If we find a significant nocturnal BP drop in patients who are on systemic hypotensives then we may ask the general practitioner or physician looking after the patient to consider adjusting the medication to avoid such a dip. In patients who are not taking antihypertensives, eliminating any nocturnal dip is therapeutically difficult. The aim in this group is to try and lower the IOP at night to correspond to the timing of the dip, so that the perfusion pressure of the eye may be improved. There is some evidence that latanaprost may be useful for this.

We have devised an algorithm to assist in the practical management of the patient with confirmed or suspected NTG (Fig 1).

**Options for treatment**

If significant and confirmed deterioration is demonstrated, then treatment options are discussed with the patients. These may be divided into (a) IOP lowering treatments and (b) non-IOP lowering treatments.

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