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MINI REVIEW

Low tension glaucoma – its place in modern glaucoma practice

One of the commonest referrals to a glaucoma unit for advice on further management is the patient with 'progressing low tension glaucoma'.[1] There is often considerable disquiet not only about the correctness of the diagnosis but also about what, if any, treatment is appropriate. In this review current ideas on the diagnosis, prevalence, and characteristics of low tension glaucoma are set out, and some of the many limitations to our knowledge noted, along with possible treatments.

Definition

Low tension glaucoma may be defined as a variety of primary open angle glaucoma, having characteristic glaucomatous cupping and field loss, an open angle, and an intraocular pressure (IOP) within the normal range, with no other cause for these changes. Strictly speaking as the IOP is 'normal' rather than 'low' it should be called normal tension glaucoma. Common usage will ensure that the older title will continue for a while yet.

When diagnosing low tension glaucoma it is necessary to remember how difficult it is to define 'normal' pressure. Mean IOP has been derived from studies of large or 'total' Caucasian adult populations. Two standard deviations above this mean would include 96% of the population and include most of the normals. For the populations studied this 'upper limit of normal' lies near 21 mm Hg. Glaucomatous disease developing in an eye with IOP at or below this level can be said to have 'normal tension glaucoma'. The arbitrariness of this definition will be seen when it is remembered that the IOP in Caucasians rises with age in line with the systolic blood pressure,[2] yet the 21 mm Hg level is taken as the average for all adults; for a young adult Caucasian this level may therefore be too high, and conversely for an octagenarian it may be too low. The problem is further confounded on translating the results for Caucasians to other populations. For example Japanese adults show a fall in IOP with age,[3] again in line with systemic blood pressure. The mean IOP for an elderly Japanese patient is lower than for his Western counterpart, and so is his upper limit of normal. There will be a far greater prevalence of low tension glaucoma in Japan if definitions of normal based on Western pressure levels rather than Japanese ones are used, and this is the case. Of greater relevance to the urban populations in the United Kingdom is the fact that while West Africans have low IOPs (with large cup/disc ratios) with large numbers of 'low tension glaucomas' some of their Caribbean descendants may not, having aquired the IOP and systolic blood pressure consequences of a Western diet.

Eyes being considered for the diagnosis of low tension glaucoma should have diurnal curve measurements to rule out pressure spikes. A past history of trauma, treatment with topical steroids, or inflammation could all point to episodes of raised intraocular tension. The nerve fibre layer type of visual field defect could originate from a lesion behind the eye. All contenders for the diagnosis 'low tension glaucoma' should be investigated with these thoughts in mind, and the diagnosis should not be considered until episodic ocular hypertension and other causes of optic atrophy have been excluded. It should be noted in passing that it can be very difficult, on the basis of a single examination, to rule out anterior ischaemic optic neuropathy as the cause of the visual loss, and a final diagnosis may have to await evidence of progression of the visual field defect.

It can be seen that the inclusion of a patient in the category 'normal tension glaucoma' should be based on local rules and that there is no sharp dividing line between normal tension glaucoma and its more common counterpart 'high tension glaucoma'. For a Caucasian patient however the presence of glaucomatous field loss and cupping in an eye with open angles and an IOP *consistently* below 22 mm Hg suggests the diagnosis of normal tension glaucoma, which would be confirmed upon progression of the visual field defect.

Prevalence

Glaucoma screening of total populations reveals a surprisingly high figure for normal tension glaucoma, figures of up to 35% of all open angle glaucomas have been reported.[4] On rescreening these eyes the IOP is often found to be above normal so the figure for normal tension glaucoma in the community falls. A truer figure for Caucasians is probably nearer 15% of all primary open angle glaucoma patients.

Characteristics

A large number of studies have been carried out comparing the features of eyes with normal tension glaucoma as defined above with eyes having high tension glaucoma. There have been no detected differences in the topography of the optic disc[5,6] but the incidence of splinter haemorrhages on the optic disc is higher in normal than in high tension glaucoma.[7,8]

Comparisons of the visual field have tended to agree that while the visual field defects in normal tension glaucoma may be more likely to show dense defects close to fixation, this is not diagnostic.[9–14] It has been suggested that the uninvolved hemifield is more likely to be 'normal' without evidence of diffuse visual loss in normal tension glaucoma.[15,16] This finding has not been confirmed by other studies and seems to have been due to the analysis method used. The nature of the visual field loss would appear the same in normal tension and high tension glaucoma.

Though there is little difference in male:female ratios in patients with high tension glaucoma, the ratio in normal tension glaucoma is 1:2. There are no apparent rheological, haematological, or vascular differences between patients with normal and high tension glaucoma.[17,18]

Subgroups of normal tension glaucoma

Greve and his group in Amsterdam have proposed that normal tension glaucoma be divided into different subgroups based on differing clinical characteristics. In so doing they have emphasised the association of normal tension glaucoma with myopia, focal ischaemic episodes, and 'burnt out glaucoma' – senile sclerotic glaucoma.[19] While this descriptive classification highlights different possibilities in pathogenesis of the disease, it remains to be seen whether the response to treatment varies from group to group.

Pathogenesis

Traditionally glaucoma was a disease of the optic nerve produced by an elevated IOP either directly, by mechanical means, or indirectly, by influencing blood supply. Recognition of progressive optic nerve disease coexisting with a normal IOP required reworking of hypotheses of causation. Today there is a wide spectrum of ideas on causation. At one extreme lie the 'mechanists' who consider normal pressure glaucoma to be a disease where the IOP is 'too high for the eye'. In support of this hypothesis is the concept that the laminar architecture is less well developed, and therefore less supportive in these eyes[20]; secondly that the collagen is different and, again, less supportive[21]; thirdly, that eyes with bilateral asymmetric disease will have a higher tension in the more advanced eye.[22 23]

The other extreme is that the optic atrophy and the IOP are manifestations of the same disease, but that one does not cause the other (it should be noted that the same theory is held for high tension glaucoma too!).[24 25] Evidence in favour of this is found with the discovery that eves with normal tension glaucoma may develop raised tension with time.[26]

A middle way exists too, suggesting that all open angle glaucomas be divided into 'pressure dependent' and 'pressure independent' types, distinguishable by certain haematological and rheological features.[27] It can be difficult to identify which patient will come into which category and therefore rationalise hypotensive treatment.

The question of pathogenesis is unresolved at the present time, and with this uncertainty comes concern about what treatment, if any, to give.

Management

Treatment for high tension glaucoma is given on the not unreasonable assumption that the high tension is at least partly responsible for the visual field loss and if the tension remains high the condition will progress. Treatment for these eyes is designed to halt, or at least slow, this inevitable progression.

As noted above it can be difficult to distinguish between eyes with an anterior ischaemic optic neuropathy and normal tension glaucoma until they progress. There is no point in treating a non-progressive disease. The first requirement in management, therefore is (a) to rule out 'retrolaminar' causes for the visual loss (remembering that a skull *x* ray is inadequate for this purpose and that if doubt exists as to the nature of the visual loss the patient should undergo a computed tomographic or magnetic resonance imaging scan), and (b) to have the wherewithal to follow the patient by assessing the optic disc and IOP, but most importantly by monitoring the visual fields.

Early attempts with kinetic perimetry using the Goldmann perimeter identified progression over 2–10 years of follow up in about 40–60% of eyes.[12 28] Progression, when it occurred, often did so in a stepwise fashion (also noted in eyes with high tension glaucoma).[29] The use of computer assisted static perimetry, especially with linear regression analysis of individual retinal test locations, allowed the identification of progression more quickly and detected it more often in these eyes.[30 31] Therefore the patient should be followed with 4–6 monthly computer assisted perimetry and the visual fields analysed by linear regression analysis of each retinal point. Using this technique it is reasonable to watch the patient without treatment until evidence of progression occurs. At least 12 months of sequential perimetry may be needed for this purpose.

The treatment given to eyes with low tension glaucoma has traditionally been standard glaucoma therapy, medical laser, or surgery.[32] In a recent review of the results of such an approach Gjiessen concluded that neither medical nor laser therapy could be relied upon to produce a significant or worthwhile lowering of IOP.[19] If IOP lowering was needed for these eyes they should undergo fistulising surgery.[19 33] This will produce a significant lowering of the IOP; what remains undecided is the effect it has in preventing further visual field loss.[33]

To date there have been no published comparative trials comparing surgery versus no surgery. Anecdotal and case reports have been optimistic.[34] In a review of their long term results deJong and colleagues in Amsterdam concluded that surgery had a protective effect.[35] At Moorfields Eye Hospital an ongoing within patient prospective study has been underway for the past 5 years. In this study one eye of 14 patients with bilateral progressive low tension glaucoma was operated upon. This resulted in a significant lowering of IOP. These patients have been followed for a mean of 46 and a minimum of 29 months. To date there has been no difference in the number of significantly worsening retinal test locations, nor in the rate of loss.

Surgery may still offer some protection against further visual loss. The Amsterdam results suggest it, the Moorfields results, so far, do not. However the mean follow up of 2·5 years is a comparatively short period of time, and the IOPs achieved, in the low 'teens, may still have been too high. The Glaucoma Foundation is coordinating a multicentre study to answer these questions. Faced with a patient having progressive normal pressure glaucoma it is still justifiable to offer fistulising surgery as an option, at least to one eye. If electing to take this route, consideration should be given to the use of 5-fluorouracil, particularly if the patient is young, black, or has already received long term topical antiglaucoma treatment before.[36 37]

What options exist other than surgery? Recently attention has been drawn to the above average incidence of migraine and associated peripheral vasospasm in patients with normal tension glaucoma.[38–41] It has been suggested that these eyes may suffer from focal arteriolar constriction in the optic nerve, with subsequent optic atrophy.[42] Calcium channel blockers, by causing smooth muscle relaxation, have been put forward as a long term treatment in such cases.[43] The calcium channel blockers in current use, such as nifedipine (Adalat), can cause significant hypotension and could be contraindicated in many of our patients for this reason. 'Second generation' drugs such as lisinopril may prove easier to use. This approach, though of theoretical value, has yet to be shown to delay let alone halt progression of this disease.

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