Regression analysis of visual field progression in low tension glaucoma

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Abstract
Eighty-four patients (168 eyes) with low tension glaucoma were prospectively reviewed (mean follow-up was 28 months). The mean age was 66 years, and 69% were females. Regression analysis of their automated Humphrey fields (a mean of eight fields per eye) showed progression in 50% of patients and in 37% of eyes. There was no statistically significant difference between patients with progression and non-progression with respect to age (p<0.05) or intraocular pressure (p<0.05). Visual field defects were located most frequently in the superior hemifield in both groups of patients. A considerable proportion of patients had advanced field loss at the time of diagnosis.

Low tension glaucoma (LTG) has always been an intriguing form of optic neuropathy. As early as 1857 von Graefe1 noted disc cupping and pallor in some eyes in the presence of normal intraocular pressure. Since then the characteristics and details of visual field defects in LTG have been studied2-4 and frequently matched and compared to those in high pressure glaucoma.4-6 Despite this there is little evidence of the natural history of field loss in LTG. In earlier studies the number of patients and fields was relatively small. Chumbley and Brubaker7 reported progression in 41% of 34 eyes (17 patients). Levene8 found the same proportion in his extensive review of 34 eyes in 23 patients. Anderston et al10 also observed 40% of 56 patients worsening when followed up for a mean of 10.5 years. Glicklich et al11 were the first to use automated perimetry to study progression in LTG. Their figure was 53% at three years and 62% at five years follow-up. All his 36 patients were on medical treatment and 65% had a surgical procedure. His analysis was made on only three fields per eye.

We retrospectively reviewed patients with LTG followed up at Moorfields Eye Hospital. Regression analysis of automated fields was performed to determine the proportion of eyes which showed definite progression.

Patients and methods
Patients with LTG followed up in the Glaucma Unit at Moorfields Eye Hospital were retrospectively looked at for the purpose of our study. Many of these patients were reported on earlier, with manual perimetry studies.11 The present report includes findings obtained with automated perimeter only.

Our criteria for diagnosing LTG were: (1) a mean intraocular pressure of 21 mm Hg or less; (2) glaucomatous optic disc cupping; (3) glaucomatous nerve fibre field loss; (4) open angle by gonioscopy; (5) absence of other ocular pathology.

Our patients were seen at three-monthly intervals. At each visit a mean of three intraocular pressure readings was obtained with the Goldmann tonometer. The anterior segments and optic discs were assessed by one of three glaucoma specialists and compared with the findings at previous visits. Humphrey automated perimetry using the central 30-2 program was also performed. Stereo optic disc photos were taken yearly. Visual fields were considered for analysis only if reliable. Reliability was defined12 by (a) absence of fixation losses; (b) a false positive rate less than 20%; (c) a false negative rate less than 20%; (d) constant stimulus and pupil size. The criterion of abnormality of fields was the presence of three contiguous points depressed by >5 decibels when compared with age matched normal persons within the central 30°.

All analysed patients met the above criteria with respect to intraocular pressure, visual fields, and optic disc appearance. Patients whose mean intraocular pressure went over 21 mm Hg during the follow-up period were excluded from the analysis. The same was true of those who developed significant lens opacities leading to poor visual testing performance.

Linear regression analysis was done on each tested retina location in the Humphrey fields of each patient. At and from the third field onwards the sensitivity of each point in decibels was compared with that of the previous field. A slope showing a change in sensitivity of less than 0.2 decibel per month was considered to denote stability. On the other hand a slope showing a decrease in sensitivity of more than 0.2 decibel per month with a correlation coefficient of significance p<0.05, was considered to denote progression (that is, worsening) in that specific point.

For the purpose of this analysis progression in a visual field was considered to have occurred if at least the last two consecutive slopes of one or more tested locations were negative (p<0.05). All other possibilities, including a single negative regression slope, were considered to indicate a static field.

The location of the visual field defects was also looked at. They were categorised as being para-central, altitudinal, or occupying a certain quadrant.

Results
Eighty-four patients (168 eyes) met the study criteria. Fifty-eight (69%) were females, giving a female to male ratio of 3:2. This is no different
from that reported in previous series.\textsuperscript{4,10,11} Their ages ranged from 38 to 86 years, mean 66 years. They all had in-hospital day phasing. Thirteen (17\%) of them had phasing repeated – once on presentation to the Glaucoma Unit at least six years before, and a second time more recently. Neurological disease was ruled out in every case. No patient was on any antiglaucoma treatment. A visual acuity of 6/12 or better was present in each eye, and no lens opacities existed at the time of field testing.

The follow-up ranged from eight to 48 months, mean 28 months. Two-thirds of the patients had been attending the LTG clinic for at least six years. The mean number of Humphrey fields per eye was eight, with a range of four to 14. All but 10 patients had bilateral field defects, the rest had unilateral defects. They were included in the study as they satisfied all other criteria. The mean IOP was 16 (15-98) mm Hg, range 7 to 26 mm Hg. (A single patient had one reading of 26 mm Hg; his mean intraocular pressure was 15-7 mm Hg over 38 months.) The distribution of patients and eyes according to their IOP means is shown in Figs 1 and 2 respectively. Forty-two (50\%) patients and sixty-two (37\%) eyes were shown to have progressed. Among those patients who progressed 20 (25\%) did so in both eyes, while 22 (26\%) progressed in one eye only. Table 1 lists the mean age and mean IOP for patients and eyes.

Statistical analysis by comparison of the means showed that there was no statistically significant difference between progressing and non-progressing patients with respect to age (p<0.5) or IOP (p<0.5). The same was true between patients showing progression in one eye and those showing progression in both (p<0.5). Progressing and non-progressing eyes showed no significant difference in their IOP (p<0.5). The mean follow-up was 28 months for patients with both progressing and non-progressing eyes.

Table 2 shows the detailed location of the field defects: (a) altitudinal (superior and inferior); (b) advanced loss (360\°); (c) paracentral (within 10\° of fixation); (d) quadratic (supero- or inferonasal, supero- or inferotemporal); (e) vertical (nasal or temporal). Fig 3 shows the same by restricting the analysis to the superior and inferior hemifields and to advanced and para-central loss.

Discussion
Linear regression analysis gave negative regression slopes significant at the 0-05 level in 50\% of patients (37\% of eyes). These figures compare well with those reported by Chumbley and Brubaker,\textsuperscript{6} Levene,\textsuperscript{8} and Anderton et al\textsuperscript{12} using manual perimetry. They are lower than the 53\% and 62\% reported by Glicklich et al\textsuperscript{11} at three and five years of follow-up respectively with computer assisted perimetry. One reason for the difference between our results and those of Glicklich et al is that we included as ‘progression’ only those eyes with evidence of continued progression on repeat testing three to six months later.

Compared with cases of high pressure glaucoma, cases of LTG scotoma were found to be closer to fixation,\textsuperscript{4,4,10,11} and to be deeper and to have steeper slopes by some authors\textsuperscript{4} but not by others.\textsuperscript{8} However, all published material agrees that the superior hemifield\textsuperscript{4,5,11} and specifically the superonasal quadrant\textsuperscript{4} are the most frequent locations for LTG defects. Our analysis (Table 2) also shows the superior hemifield to be mostly affected in both non-progressing and progressing eyes (40\% and 52\% respectively). Advanced loss (360\°) was found in 21\% and 18\% respectively. This comes as no surprise. Being asymptomatic in terms of IOP, LTG patients are discovered late in the course of their disease. A number of eyes (4\% of non-progressing and 13\%
of the progressing ones – Table 2), have been found to have defects respecting the vertical axis or meridian. This has not been observed before, and it might be partly due to the grouping of test locations by the Humphrey field analyser.

Having confirmed that a high proportion of eyes with low tension glaucoma worsen over comparatively short periods of time, the question arises, what can be done about it? At the present time the favoured approach is to try to delay progression by lowering the IOP. The most published method for this is by fistulising surgery.

Surgery in the management of LTG is well known. Among others, Bloomfield and then Levene realised that progression maintained its same pace despite successful surgery. Hitchings commented on the difficulty of maintaining a significantly low pressure in these patients. de Jong et al reported reducing the number of eyes with continued progression to only 8% following a 20% reduction in IOP in 26 eyes of 20 patients with a follow-up of three years.

It should be noted, however, that the patients of de Jong et al had a mean preoperative IOP of 22 mm Hg. In contrast, the mean IOP for the patients in this series was only 16 mm Hg, making the task of IOP lowering that much harder. Another problem which occurs in the assessment of the efficacy of IOP lowering as an agent of halting visual loss is the suggested episodic nature of progression. In their long term follow-up of patients with low tension glaucoma Anderton et al noted this episodic progression occurring, and that the mean interval between periods of progression was 4-4 years.

In the absence of any tested alternative for the treatment of low tension glaucoma it is important to assess the hypothesis that progressive visual loss in this disease occurs because the IOP is too high for the eye and to run a trial of treatment versus no treatment. Such studies are now under way.