

Comparison of visual field progression in patients with normal pressure glaucoma between eyes with and without visual field loss that threatens fixation

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Abstract

Aim—To compare the frequency and site of visual field progression and changes in visual acuity in patients with normal pressure glaucoma (NPG) with and without pre-existing visual field loss.

Method—Patients with normal tension glaucoma were selected who had at least 10 visual fields over 5 or more years of follow up and no other condition that might influence the visual field or visual acuity. Alternate left and right eyes were selected from patients in random order. These eyes were then subdivided according to visual field defect threatening fixation, visual field defect not threatening fixation, and no visual field defect (fellow eyes). Eyes were defined as showing a threat to fixation according to the presence of a visual field defect involving one of more of four paracentral visual field locations. Pointwise linear regression analysis was applied to each visual field series using PROGRESSOR software. Progression of visual field loss was defined as the appearance of a regression slope 1 dB per year or more with a significance of $p < 0.01$, which remained consistent with the addition of two of three successive visual fields to the series. The number of patients showing progression and the number where progression occurred in one of the four paracentral visual field locations was noted. The number of eyes losing two or more lines of Snellen visual acuity over the follow up period was also noted.

Results—174 eyes of 174 patients were selected. 106 eyes had visual field loss threatening fixation, 46 eyes had visual field loss that did not threaten fixation, and 22 were fellow eyes with normal visual fields. The median follow up was 7.2 years. Eight eyes (36.4%) in the “normal visual fields” group, 31 eyes (67.4%) in the “visual field loss away from fixation” group, and 87 eyes (82.1%) in the “threat to fixation” group showed progression in any part of the visual field. Two eyes (9.1%) in the “normal visual fields” group, nine eyes (19.6%) in the “visual field loss away from fixation” group, and 45 eyes (42.5%) in the “threat to fixation” group showed progression at “threat to fixation”. The Cox proportional hazards regression model showed an increased risk of progression at any part of the visual field for female sex and a decreased risk

for eyes with normal visual fields. For progression at threat to fixation this model showed an increased risk with pre-existing threat to fixation. Eyes from older patients and those that went on to have progressive visual field loss at fixation were more likely to lose two lines of Snellen visual acuity over the follow up period. **Conclusion**—Since 20–30% of previously field damaged eyes and over 60% without prior field loss fail to demonstrate progressive visual field damage over a long follow up it is recommended that normal pressure glaucoma patients be monitored for progression and that potentially harmful therapy be withheld until progression is demonstrated. Although the presence of visual field loss that threatens fixation does not constitute an increased risk of visual field progression it does indicate an increased risk of further loss of visual field close to fixation which is in turn associated with loss of central acuity. In the light of this finding, patients with visual field loss that threatens fixation should be managed more aggressively.

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Normal pressure glaucoma (NPG) has a prevalence of 0.6% within white populations and is thought to account for 20–30% of primary open angle glaucoma.^{1–3} It is characterised by an intraocular pressure that is found to be within the normal range together with cupping of the optic nerve head and visual field loss of a nerve fibre layer type.

The presence of visual field loss that comes close to fixation, so called “threatened” or “split” fixation, is of concern when managing glaucoma patients. Previous studies have shown that high tension glaucoma (HTG) patients with visual field defects which involve the central 5° of the visual field are at greater risk of losing visual acuity.^{4–5} Visual acuity loss has also been shown to be more likely in these patients in the presence of inadequately controlled intraocular pressure (IOP).⁴

Differences in the type of visual field loss seen in NPG compared with HTG have been suggested by several investigators.^{6–12} It has also been shown that in NPG both central visual field loss, involving the central 10° field, and more peripheral field loss are related to the level of IOP.¹³ What has not been established is whether the proximity to fixation of visual field loss relates to the likelihood of disease progres-

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sion and the likelihood of deterioration in central visual function in NPG.

The purpose of this study was to compare the frequency and site of visual field progression and changes in visual acuity in NPG patients with and without pre-existing visual field loss that comes close to fixation.

Materials and methods

The hospital records of all patients attending the NPG clinic at Moorfields Eye Hospital who had at least 5 years of follow up with at least 10 automated visual field tests were reviewed. All patients who satisfied the following criteria for NPG were included in the study.

NPG was defined as the presence of (1) glaucomatous cupping of the optic nerve head; (2) untreated mean phasing IOP no greater than 21 mm Hg and no single reading greater than 23 mmHg; (3) the presence in either eye of a minimum visual field defect as defined below.

For each eye the following patient data were collected: age; sex; mean phasing IOP; median of the mean deviations from the first three visual fields (start MD); type of treatment and date treatment first started; the presence of any other ocular condition that might affect visual acuity or visual field.

Eyes were excluded where diagnoses other than glaucoma, which might affect the visual field or visual acuity, had been made.

Where both eyes from a patient were eligible only one eye was included in the study; these were determined by taking alternate left and right eyes from these patients in random order.

VISUAL FIELD ANALYSIS

Visual field testing was done on the Humphrey visual field analyser (Humphrey Instruments Inc, San Leandro, CA, USA) using the 24/2 or 30/2 programs. The first two tests were ignored in all subsequent analyses to allow for learning.

A minimum visual field defect was defined as the presence in one hemifield of a cluster of at least three points depressed by 5 dB from the perimeter's database of age matched normal values, with at least one point depressed by ≥ 10 dB. This had to be consistent in the first three visual field tests. If one or more of these depressed points involved one of the four paracentral test locations these eyes were defined as having "threat to fixation". The four paracentral locations are those at coordinates $-3,+3-3$, $-3+3$, $+3$, and $+3,-3$. If none of the four paracentral locations were involved these were defined as "field loss away from fixation".

If an eye did not meet the minimum visual field defect criteria above these were defined as "normal visual fields".

Our standard management has been to follow NPG patients without treatment until visual field progression is detected, visual field testing being performed every 4–6 months.¹⁴

Pointwise linear regression analysis was applied to the field series of the study patients using PROGRESSOR for windows software.¹⁵ Progression was defined as the presence of a significant regression slope ($p < 0.01$) showing 1 dB per year or more of sensitivity loss at the same test location with the addition of two out of three successive field tests to the series starting with the first three. Only the locations from the 24/2 visual field were considered. If one or more of the four paracentral test locations was found to be progressing this was defined as "progression at threat to fixation". If progressing locations were identified that did not involve any of the four paracentral locations this was defined as "progression away from fixation". The date of the first visual field to be added to the series that allowed progression to be detected was recorded as the date of progression. Eyes were censored after progression had been confirmed.

VISUAL ACUITY

The median of first three and last three best corrected or pinhole Snellen visual acuity scores were recorded. Eyes that lost two or more Snellen lines of visual acuity or worsened by one low vision category (low vision categories were counting fingers, hand movement, light perception, and no light perception) were identified and recorded as "visual acuity failures".

Baseline characteristics were compared between different visual field groups using χ^2 or Kruskal–Wallis tests. Data on visual field progression at any location and at "threat to fixation" were analysed using survival analysis techniques. Kaplan–Meier plots were constructed and Cox regression analysis was performed to assess the relative influence of baseline data on the risk of visual field progression. Logistic regression analysis was used to assess the association of baseline data and the type of visual field progression with "visual acuity failure". Analyses were conducted using the Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL, USA) for windows (version 8.0; Microsoft Corporation, Redmond, WA, USA) and Stata Statistical Software Release 5 (Stata Corporation, USA).

Table 1 Demographic data and data on length of follow up and number of visual fields by visual field group

	Normal field (n=22)	Field loss away from fixation (n=46)	Threat to fixation (n=106)	p Value
Left eyes	7 (31.8%)	28 (60.9%)	55 (51.9%)	0.081*
Female sex	11 (50%)	26 (56.5%)	71 (67.0%)	0.218*
Age median (IQ range)	67.0 (62 to 75)	69.0 (65 to 73)	73 (66 to 77)	0.083**
MD start median (IQ range)	-1.7 (-3.1 to -0.2)	-5.1 (-9.3 to -1.6)	-10.7 (-16.6 to -7.0)	<0.001**
Number of visual fields median (IQ range)	15.5 (12 to 21)	18.5 (14 to 23)	18.0 (16 to 23)	0.251**
Follow up in months median (IQ range)	93.3 (66.6 to 114.6)	96.6 (75.9 to 119.9)	85.7 (71.7 to 108.6)	0.3**

* χ^2 test used, **Kruskal–Wallis test used.

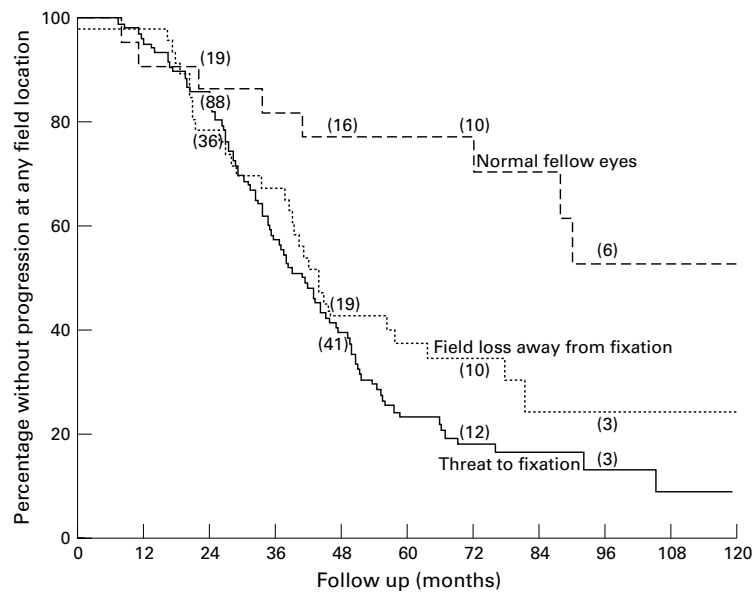


Figure 1 Survival plot where survival is defined as lack of progression at any field location, groups defined by initial field group. (n=number surviving.)

Table 2 Risk of progression in any part of the visual field compared with “visual field loss away from fixation” group

	Hazard ratio	CI	p Value
Visual field loss away from fixation	1.00		
Threat to fixation	1.32	0.88 to 2.00	0.18
Normal visual held	0.35	0.16 to 0.77	0.009
Female sex	1.6	1.1 to 2.34	0.014

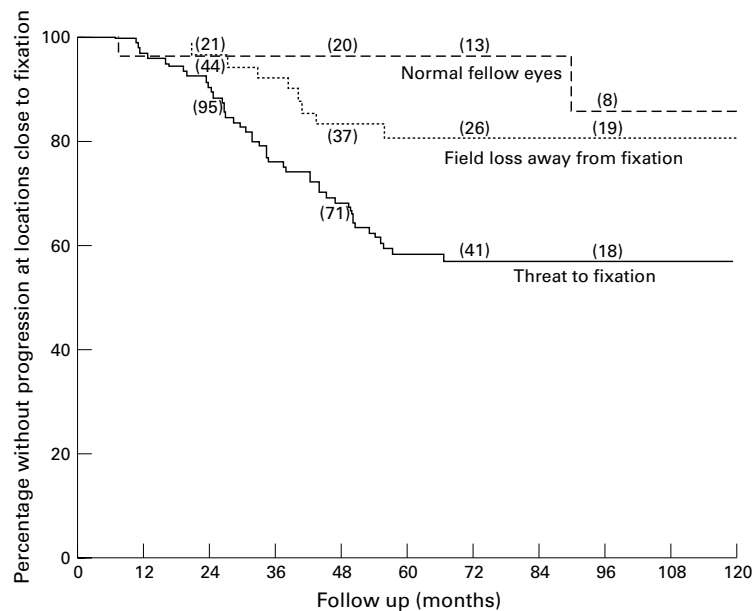


Figure 2 Survival plot where survival is defined as lack of progression at locations close to fixation, groups defined by initial field group. (n=number surviving.)

Table 3 Risk of progression at threat to fixation compared with “visual field loss away from fixation” group

	Hazard ratio	CI	p Value
Visual field loss away from fixation	1.00		
Threat to fixation	1.87	1.21 to 5.08	0.032
Normal visual field	0.43	0.09 to 1.98	0.291

Results

In all, 367 eyes of 185 NTG patients were identified with 10 or more visual field tests performed over 5 or more years of follow up. The median follow up period was 7.2 years. Twenty nine eyes of 18 patients had other ocular diagnoses which might affect visual acuity or the visual field (for example, age related macular degeneration, cerebral vascular accident) and were therefore excluded. This left 338 eyes of 174 patients. After random selection as described there were 174 eyes (90 left and 84 right) of 174 patients. By the above definitions: 106 eyes had “threat to fixation”; 46 eyes had “visual field loss away from fixation”, and 22 had “normal visual fields”. There was no significant difference between the groups in the number of visual fields or length of follow up (see Table 1).

Eight eyes (36.4%) in the “normal visual fields” group, 31 eyes (67.4%) in the “visual field loss away from fixation” group, and 87 eyes (82.1%) in the “threat to fixation group showed progression in any part of the visual field.

Two eyes (9.1%) in the “normal visual fields” group, nine eyes (19.6%) in the “visual field loss away from fixation” group, and 45 eyes (42.5%) in the “threat to fixation” group showed progression at “threat to fixation”.

The Cox proportional hazards regression model was used to assess the influence of visual field type, age, start MD, sex, mean diurnal IOP, and whether treatment was started before progression on visual field survival. Progression was defined both as that occurring in any part of the visual field and at “threat to fixation”.

One hundred and one eyes were treated at some stage during the follow up period; 69 of these eyes had only medical treatment which consisted of one or more of the following—topical α agonists; β blockers; pilocarpine, and systemic calcium channel blocking medication. Thirty two eyes had drainage surgery with or without medical treatment; 25 (14.4%) eyes had treatment before progression. The Cox model showed that these data provide little evidence of any effect of previous treatment or the form this took on the risk of progression.

For progression in any part of the visual field this model showed a greater hazard for female eyes and a lower hazard for eyes in the “normal visual fields” group (see Fig 1 and Table 2).

For progression at threat to fixation this model showed a greater hazard for eyes in the “threat to fixation” group see Figure 2 and Table 3.

Logistic regression analysis was used to assess the association between baseline data (visual field type, age, start MD, sex), type of treatment and type of visual field progression at end point with “visual acuity failure” as defined above.

Table 4 Factors associated with “visual acuity failure” (only those where $p < 0.1$ are shown)

	Odds ratio	p Value
Progression at threat to fixation	5.07	0.029
Age	2.22	0.027

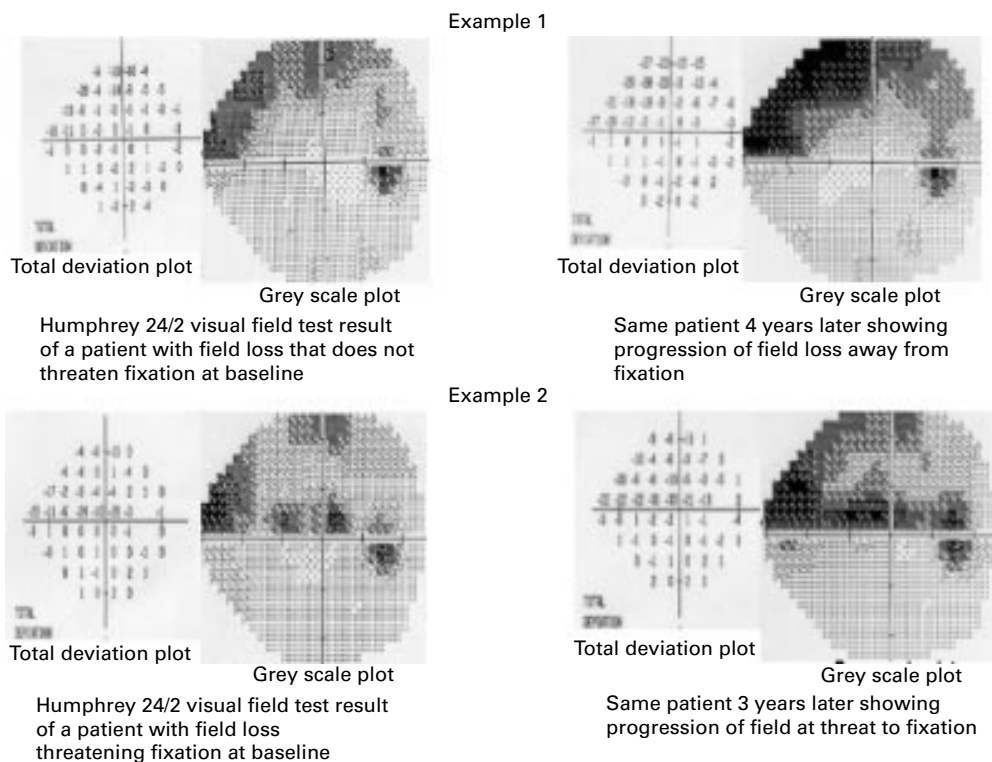


Figure 3 Humphrey 24/2 visual fields from two patients. Example 1 is of a patient with visual field loss away from fixation at the start of follow up (top left) who shows progression away from fixation at the end of a 4 year follow up period (top right). Example 2 is of a patient with visual field loss threatening fixation at the start of follow up (bottom left) who shows progression at threat to fixation at the end of a 3 year follow up period (bottom right).

This model showed an increased risk for eyes from older patients and those that went on to have “progression at fixation” (see Table 4).

Six (10.1%) of those eyes showing progression at threat to fixation also had a “visual acuity failure” compared with three (2.4%) of those eyes that showed progression away from fixation and none of those that did not show any progression (see Fig 3).

Discussion

This paper reports on the incidence of visual field progression in a series of patients with NPG who were largely untreated before progression and followed for a median of 7 years. It found that eyes with normal visual fields were less likely to show visual field progression than previously field damaged eyes; 36.4% of these showed progression in this study and this figure is similar to that previously reported¹⁶; 77.6% of previously field damaged eyes showed progression in some part of the visual field. Female sex was a risk factor for progression at any field location.

Eyes from older patients were more likely to lose visual acuity over the follow up period.

The proximity to fixation of pre-existing visual field damage did not influence the risk of progression occurring at any visual field location. However, the presence of a visual field defect close to fixation does increase the risk of symptomatic progression, as this is more likely to be close to fixation. Progression of visual field loss close to fixation is also associated with visual acuity loss.

The collaborative NTG study group reported 25 of 79 (31.6%) patients in their

untreated control group showing progression by their protocol definition.¹⁷ This may seem to be very different from the results of this study of 77.6% showing progression. However, their figure does not take account of censored data. Although they state that most of the patients in the control group were followed for 5 years or more they do not give the median follow up time which was probably much less than the median of 7 years follow up in this study. In fact, direct comparison of their survival plot, which does take account of censored data, with ours shows a more similar rate of progression than this figure would suggest. It appears that 40% progressed by just over 3 years and approximately 60% progressed by 5 years. This compares with 40% progressing at just over 3 years and 66% progressing at 5 years in our study (see Fig 1). There were only 29 eyes with prior threat to fixation in their control group making separate analysis of the behaviour of this group difficult. The figures for progression in previously field damaged eyes is also similar at 5 years to the figure of 62% previously reported by Gliklich *et al* for NPG patients.¹⁸ This may be surprising as all of their 36 patients had treatment to reduce IOP and 44% achieved a 20% or more reduction in IOP from baseline. This might be explained by a lack of treatment effect or differences in the definition of progression or characteristics of NPG patients between this study and ours.

The criteria for progression in this study is the same as that used by us clinically and has been derived from previous studies comparing pointwise linear regression with STATPAC-2

change probability analysis in a similar group of patients.^{15–21} Our standard management has been to withhold treatment until or unless visual field progression occurs. This approach has given us the opportunity to study the natural history of NPG in a large group of patients. Less than 15% of eyes had treatment before progression; this was not found to significantly influence the risk of progression, although strict criteria for target IOP reduction were not followed. The reasons for starting treatment in these cases were subjective deterioration of visual field loss or patient preference, especially when patients were already being treated when referred to the NTG clinic. It should be remembered that many of our patients were elderly and who, with a slow rate of progression, would not be expected to suffer visual symptoms from glaucoma in their lifetime.

This is a retrospective review of a large number of NPG patients referred to a single hospital based glaucoma service. Diagnostic criteria for NPG were very similar to that of previous studies.¹⁷ We included only one eye from each patient in this study in order to avoid any potential overrepresentation of risk factors that may be common to both eyes. As with all hospital based studies it suffers from the same potential referral bias in NPG. This bias is likely to be different in HTG. NPG patients may be referred because an abnormal appearance of the optic disc has been found or the patient is aware of a scotoma whereas HTG patients may be referred because an elevated IOP has been found. This bias might predispose to a larger proportion of patients with localised paracentral visual field defects in NPG patients referred to hospital compared with the population of NPG patients in the community. The potential difference in bias between NPG and HTG makes interpreting any difference in the pattern of visual field loss as an indication of differences in pathogenesis unsound. However as the purpose of this study was to investigate the natural history of visual field progression in a cohort of NPG patients within the hospital glaucoma service the patient cohort was satisfactory.

Because changes in visual acuity were observed over the entire follow up period they may have been influenced by other factors such as treatment type. Previous studies have shown that patients undergoing filtering surgery are more likely to develop cataract.¹⁷ This may in turn reduce visual acuity. However, multivariate analysis did not show an effect of treatment type on visual acuity loss. The factor that showed the greatest association with visual acuity loss was progression at threat to fixation. Eyes with this type of progression were more than five times as likely to have lost two lines of Snellen acuity than those eyes that did not show progression at threat to fixation. Because of the retrospective nature of this study it is not possible to rule out the effects of unknown confounding factors. These results need to be confirmed in a prospective study.

Some 20–30% eyes with pre-existing glaucomatous visual field defects fail to demonstrate visual field progression over a long follow up

period. Since these eyes are unlikely to benefit from therapeutic intervention we would recommend that potentially harmful therapy be withheld until visual field progression is demonstrated.

However, in following NPG patients with threat to fixation a higher sensitivity and lower specificity for progression should be adopted. As previously suggested detailed examination of the paracentral field (for example, 10/2 program) would be of benefit in these cases to establish how close to fixation the field defect comes and therefore better estimate the risk of central visual loss.²² In some cases treatment before visual field progression might be justified when taking into consideration other factors such as the state of the other eye.

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