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CLINICAL STUDY

Is poor life expectancy a predictive factor in the progression of primary open angle glaucoma?

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Abstract

Aim **To investigate the disease progression and final visual outcome of glaucoma patients with poor life expectancy, compared to matched patients with a longer life expectancy.**
Method **Visual fields at diagnosis and at the last ophthalmic appointment before death were analysed for glaucoma patients referred between 1991 and 1995, and deceased before the end of 2001. These patients were matched to the patients living beyond 2001. Functional vision was also assessed, and classified as better than the NHS partial sighted criteria.**
Results **A total of 61 deceased patients were identified, resulting in 40 matched pairs. In all, 6.5% of the patients with poor life expectancy progressed from functional vision to beyond partial sighted criteria, and none of the matched patients progressed to this extent. At final assessment an association between poor life expectancy and progression beyond functional vision was found existing ($P = 0.02$), with a lesser association at diagnosis ($P = 0.06$). Visual field scores of the matched pairs who had test results available for both initial and final assessment ($n = 23$ pairs) showed no statistically significant difference between the two groups at diagnosis ($P = 0.52$); However, a significant difference at final the assessment did exist ($P = 0.042$). No difference between the initial (off medication) intraocular pressures (IOPs) was found ($P = 0.82$). At the final assessment a significant difference existed ($P = 0.025$), with the surviving group having a higher final mean pressure (15.9 mmHg, SD 2.8, *vs* 18.3 mmHg, SD 4.9).**
Conclusion **Patients with poor life expectancy progressed more than the matched surviving patients, when measured from an initially similar position, despite better IOP control.**

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Introduction

Chronic glaucoma is a progressive disease. It has been suggested that in untreated glaucoma, blindness will occur in an average of 14.4 years with intraocular pressures (IOPs) between 21 and 25 mmHg, and 6.5 years for pressures between 25 and 30 mmHg.[1] Even on treatment, an estimated 9% of the patients will become bilaterally blind after 20 years of treatment.[2] Some studies have considered glaucoma and its relationship to shortened survival,[3–7] Others have considered the effects of systemic disease on glaucomatous progression.[8,9] These studies, however, do not consider poor life expectancy as a factor in glaucomatous progression.

Patients with poor life expectancy tend to be excluded from many studies, due to protocol criteria or social/travel problems. To our knowledge, this group of patients has not been studied in any detail regarding their final visual outcome or progression of the disease while under hospital care. With functional vision for life being the ultimate aim for all glaucoma patients under hospital care, this patient group needs to be considered. This study is a case–control study, matching patients to others with a longer life expectancy.

Method

Newly diagnosed patients, referred to a glaucoma clinic from the community between January 1991 and December 1995, in a large

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teaching hospital were reviewed as to their life status at the end of 2001. Deceased patients were identified by using the hospital's computerised 'Patient Administration System'. For patients whose status was unclear (no hospital visit within 1 year, but not identified as deceased), true status was determined by direct contact with their general practitioner. Patients known to be deceased were then matched for year of diagnosis and age at diagnosis ($\pm$4 years) to patients alive at the end of 2001. The live patients were also required to have survived at least a year longer than the deceased matched patient. Deceased patients (poor life expectancy) will be known as group 1, with their matches being group 2. Comparisons were then made regarding the initial and final visual status, where the 'final' visual status of group 2 patients were considered as the nearest visual field test within a year of group 1 patients' last appointment.

Visual fields and assessment of functional vision formed the basis of the study. Visual fields were only used if they were dated within a year of diagnosis, or within a year of group 1 patient's final ophthalmic appointment. Owing to the variety of visual fields used, (Friedmann, Goldmann, Humphrey 24-2, Humphrey 76 point) all were analysed using the staging system as described by Aulhorn *et al*[10] (Table 1).

The visual fields were scored independently by two observers, a research nurse (CT), and a senior trainee ophthalmologist (AN), who was masked to the life status of the patients. All scores for visual fields were in agreement (Kappa score: 1).

The criteria for functional vision in this study was based on the NHS guidelines for partial sight registration. Vision considered as being incompatible with daily functioning was therefore based on a visual acuity of 6/24 or less, with moderate contraction of their visual field, or a visual acuity of 6/18 or better with a gross visual field defect in the patient's better eye. In assessing the initial and final visual field scores, only the patient's better eye was used; this is because functional vision requires only one eye, and the emphasis of care for an individual patient may be to keep functional vision in one eye, while keeping the other comfortable. Using a random eye, or a mean score would therefore wrongly bias the results. The initial best eye was therefore not necessarily the best eye at the final assessment. The majority of statistical analysis, including visual field analysis, was conducted using the Wilcoxon signed rank test for matched pairs. The χ^2 test was also employed when considering functional vision.

Results

In all, 123 patients were identified as deceased. Of these 78 were diagnosed with a classification of glaucoma or ocular hypertension, with one patient having rubeotic glaucoma in one eye and CSG in the other (Table 2).

Rubeotic and angle closure glaucoma patients were excluded from the study, due to the lack of data for analysis, and the variation in the underlying cause. Ocular hypertensive patients were also excluded. Pseudoexfoliative glaucoma was considered within the analysis. No patient with pigmentary glaucoma were identified. Matching was made without the knowledge of visual or glaucomatous status. Owing to the study criteria of matching patients by age and year of diagnosis, only 40 of the remaining 61 patients could be matched to surviving patients, and made up the study cohort. The mean age of the deceased patients at diagnosis was 74.7 years (95% confidence interval 72.7–76.7). For surviving patients, it was 74.3 years (95% confidence interval 72.4–76.2). The age range of deceased and surviving patients at diagnosis is shown in Figure 1. Deceased patients spent an average of 4.2 years under hospital care (95% confidence interval 3.5–4.9).

IOP

IOP was assessed at presentation in order to identify any disparity between the group 1 and 2's level of glaucoma off treatment. The mean initial IOP of group 1 was 25.5 mmHg (SD 9), with group 2's being 24.9 mmHg (SD 6.6). The matched mean initial IOPs were compared using the Wilcoxon signed rank test. No statistically

Table 1 Aulhorn visual field staging system

Stage 1 Exclusively relative defects
Stage 2 Spot-like or arcuate absolute defects, still without connection to blind spot
Stage 3 Arcuate absolute defects connected to blind spot, with or without a nasal break through into the periphery
Stage 4 Extensive ring-or half-ring-shaped defects, keeping central island of sensitivity
Stage 5 Central island collapsed, and only the peripheral temporal visual field is kept

Table 2 Classification of glaucoma in deceased cohort

	n *(Patients)*	n *(Eyes)*
Chronic simple (CSG)	48	93
Normal tension (NTG)	10	20
Pseudoexfoliative	3	6
Rubeotic	2	2
Acute angle closure	2	2
Ocular hypertension	13	26
Total	79	151

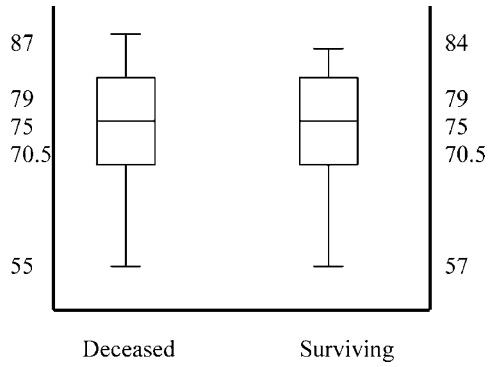

Figure 1 Age range of patients at diagnosis.

significant difference was found ($P = 0.8$). There was, however, a significant difference at final assessment ($P = 0.025$), where group 1's mean pressure was 15.9 mmHg (SD 2.8), and group 2's was 18.3 mmHg (SD 4.9). All IOPs were recorded in the morning.

Progression-functional vision

No patient from group 2 progressed from functional vision at diagnosis to fulfilling the partially sighted criteria at the final assessment. However, 6.5% ($n = 2$) of group 1 patients, with functional vision at diagnosis progressed beyond functional vision. The χ^2 test was applied to the 40 matched pairs, in order to identify any association between life expectancy and functional vision. This was conducted at diagnosis ($P = 0.06$), and final assessment ($P = 0.02$). A greater association therefore, existed at the final assessment.

Progression-visual fields

Using the Wilcoxon signed rank test, the matched visual field scores of patient's better eyes were examined at diagnosis, and at the final assessment, in order to identify any difference between the progression of the disease in the two groups. Only matched pairs, where both the patients could be assessed at initial and final assessments were used, this resulted in 23 matched pairs. The mean initial visual field scores of groups 1 and 2, respectively was 1.13 (SD 1.1) and 1.13 (SD 0.5) with a significance using the Wilcoxon signed rank test of $P = 0.52$. At the final assessment the mean scores were 1.4 (SD 0.9) and 0.9 (SD 0.6) with a significance of $P = 0.042$. In order to ensure that a valid comparison of matched patients was used, the time lapse between first and last visual field tests was assessed. The median time for groups 1 and 2 respectively was 47 months and 43 months. The Wilcoxon signed rank test, showed no significant difference between the two groups ($P = 0.2$).Visual field scores for deceased patients who were not matched but had available visual fields, were compared to the scores of the deceased matched patients. This was carried out to ensure that no bias was present in the analysis of the matched progression. Comparison was made at initial assessment (mean 1, SD 0.93) $P = 0.2$, and at final assessment (mean 1.3, SD 0.95) $P = 0.49$. There was therefore no significant difference between these groups.

The Wilcoxon signed rank test was used to identify any significant difference between the reliability indices of the matched pairs' final visual fields; this was conducted to ensure that the comparisons were valid. When considering fixation losses ($P = 0.32$), false-positive errors ($P = 0.22$), and false-negative errors ($P = 0.84$), Of the 23 pairs, seven could not be quantitatively assessed for reliability, due to the use of Friedmann visual fields; however, none of the deceased group was classed as 'poor' by the operating technician. There was therefore no significant difference between the reliability indices of the two groups.

Possible variables

A number of variables may have had an influence on the results of the progression analysis. Data on these variables were therefore assessed, which included surgery (Table 3), medication (Table 4), and gender (Table 5).

Discussion

Of the studies that have examined glaucoma and its relationship to shortened survival,[3–7] the majority showed some association.[3,5–7] One study[5] showed the lowest survival rate to be among males using acetazolamide. In our study, of the 23 pairs of patients who could be considered for visual field progression, the male/female mix in each group was identical (Table 5). In examining the use of medication at the final assessment, no patient in groups 1 or 2 was using acetazolamide, and both the groups were using a mean of 1.25 topical medications each day. The finding of increased usage of topical beta blockers in the survivors

Table 3 Ophthalmic surgery in matched pairs

	Cataract surgery	*Glaucoma surgery*	*General anaesthetic*	*Local anaesthetic*
Deceased (group 1)	9	12	3	12
Surviving (group 2)	5	9	1	12
Wilcoxon test (*P*)	0.3	0.58	0.37	1

Table 4 Ophthalmic medication in matched pairs

	Latanoprost	*Beta-blocker*	*Miotic*	*Alphagan*	*CAI's*	*Total*
Deceased (group 1)	9	17	11	2	10	49
Surviving (group 2)	11	27	3	0	8	49
Wilcoxon test(*P*)	0.66	0.048	0.058	1	0.67	

Table 5 Gender in matched pairs

	Female	*Male*	*Total*
Deceased (group 1)	10	13	23
Surviving (group 2)	10	13	23

is interesting (36 *vs* 54%, $P = 0.048$). No morbidity from the use of such agents was reported in the 'ocular hypertensive treatment study',[11] but these drugs do have recognised systemic effects, particularly in the elderly.[12] A possible reason for the increased use of beta blockers in the surviving group (group 2) could have resulted from the reluctance by ophthalmologists to prescribe such agents for patients in group 1, possibly due to medical conditions, such as asthma, which were not recorded in the medical notes. These unrecorded medical conditions could have contributed to the shortened survival, or indeed to the progression of the disease, as vascular and respiratory factors have been linked to glaucoma.[8,13–16] This reluctance to prescribe beta blockers could explain an increased use of pilocarpine in those who did not survive. A possible consequence of the increased use of pilocarpine could have resulted in the worsening of the visual field scores seen in group 1, due to the adverse effect of the drug on the patients' visual fields,[17–19] or the poorer intraocular lowering effect of pilocarpine than beta blockers.[20,21] No other classification of eye medication was significant in its use between groups (Table 4). The χ^2-test was used in order to investigate the hypothesis that the use of pilocarpine is associated with the visual field progression in group 1. There was, however, no such association in our study ($P = 0.6$). Repeating this study, using a baseline in the mid- to late 1990s after the introduction of new topical medications, such as prostaglandin analogues, and the subsequent reduction in the use of pilocarpine, would therefore be of interest. Some studies have considered shortened survival among other ophthalmic conditions. In researching patients with cataracts, it has been shown that cataracts can be linked to the shortened survival.[4,22,23] One study[24] showed a link between cataract surgery and shortened survival in middle-aged patients. It is unclear, however, whether this was due to the cataract or the surgery. In our study, there was no

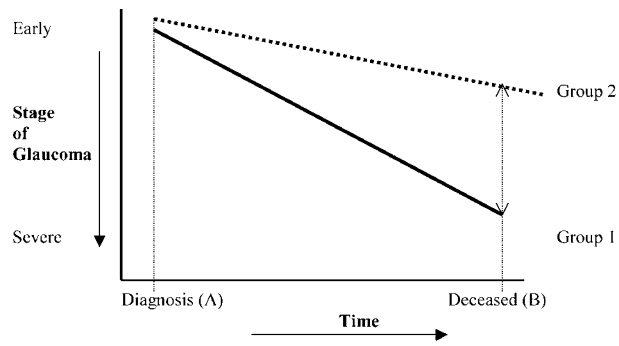

Figure 2 Model of glaucomatous progression.

significant difference between the rate of cataract surgery (including phacotrabeculectomy) $P = 0.3$, glaucoma surgery (including phacotrabeculectomy) $P = 0.6$, or type of anaesthetic ($P = 0.37$ for general anaesthesia) between the groups (Table 3).

Matched IOPs only show a difference at the final assessment (initial $P = 0.8$, final $P = 0.025$), with group 1 having lower pressures. Lowering of pressures in these patients is therefore attainable, but with a higher rate of progression also in this group, it could be suggested that factors other than the pressure are greatly influencing the outcome, within this group.

The statistical tests used show a greater progression of glaucoma in patients with a poor life expectancy, but a similar presenting stage. These results may be explained by considering glaucomatous progression as being on a progressive downward slope. Patients with a poor life expectancy (group 1), may be on a steeper gradient throughout the course of their disease, than the surviving matched patients (group 2). These slopes may therefore be diverging throughout time (Figure 2). Assessments at point (A) will give an insignificant difference, whereas at point (B) a significant difference is evident. Data for this study were taken retrospectively from the medical notes, and is therefore limited to information, which was deemed necessary to record at the time of attendance.

The numbers used in this study are small, with the possibility of results being biased by very few patients in group 1 having unstable glaucoma. With the cohort being the maximum that the protocol would allow, much larger multicentred, case–control studies are required, with in-depth analysis of the patients' medical condition,

systemic medications, cause of death, medication compliance, social history, and ethnic origin. Further research into the systemic conditions and their impact on glaucomatous progression is needed. A possibility could involve the circulatory system of the patients condition, as it is not only the largest cause of death in the UK,[25] but has also been proven to have a role in glaucoma.[8,13,14] Such studies will be made easier to perform with the use of electronic data management systems, such as Eyetrack[26] in which health-care professionals are prompted to record data on general health. If larger studies were to confirm our results, the impact may well be to shift practice towards a more holistic, systemic focus of glaucoma management.[27]

With functional vision for life being the ultimate aim in ophthalmology, it would be useful to assess the patients' quality of life, possibly by a social assessment, or direct questioning, rather than making a decision based on previously considered disease progression and mortality.

This case–control study has shown a link between the worsening of glaucoma and reduced survival. It is unclear, however, whether glaucomatous progression is a cause of, a result of, or a marker for reduced life expectancy.

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