Natural History of Open Angle Glaucoma

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Abstract

Objective: This paper, based on the Early Manifest Glaucoma Trial (EMGT), provides prospective natural history data on progression of glaucomatous field defects in three of the most common glaucoma types.

Design: Cohort of EMGT patients randomized to the untreated control group and followed up to the time of progression, when treatment could be initiated.

Participants: We evaluated 118 control patients: 46 with "high-tension" glaucoma (HTG), 57 with "normal tension" glaucoma (NTG) and 15 with pseudoexfoliation glaucoma (PEXG).

Methods: Visual fields were tested every 3 months with the Humphrey 30-2 Full Threshold test program.

Main Outcome Measures: Linear regression analyses of the perimetric mean deviation (MD) values were performed and the rate of progression defined as the regression coefficient in dB/year. Percentages of progressed eyes and time to progression were determined using EMGT event-based predetermined progression criteria derived from Glaucoma Change Probability Maps.

Results: The median and interquartile rates of visual function loss were -0.40 (1.05) dB/year overall, and were -0.46 (1.61) in HTG, -0.22 (0.65) in NTG and -1.13 (6.13) in PEXG. Thus, inter-patient variability was large. Mean rates were considerably higher than medians: -1.08 dB/yr overall, -1.31 in HTG, -0.36 in NTG and -3.13 in PEXG. Differences in median VF progression rates among groups were statistically significant (NTG vs. HTG, P=0.003; PEXG vs. non-PEXG, P<0.001). Progression was considerably and significantly faster in older than in younger patients (P=0.002). By 6-years, 68% of patients had progressed overall, 74% of HTG, 56% of NTG, and 93% of PEXG patients (P=0.012). Median time to progression also differed considerably among groups: 19.5 months in PEXG, 44.8 months in HTG, and particularly 61.1 months in NTG (P<0.0001).

Conclusions: In this 6-year follow-up study, the median untreated rate-of-progression corresponded to advancing from normal visual function to blindness in approximately 70 years, while based on the mean rate, visual function would show the same deterioration in approximately 25 years. Large differences existed among patients, and also among different glaucoma types with PEXG progressing considerably faster than POAG, and NTG progressing at the lowest rate.

Introduction

Data on the natural history of visual function deficits in glaucoma are very limited. This is expected, since pressure-reducing therapy is usually instituted without delay in patients with diagnosed glaucoma with visual field defects, except sometimes in glaucoma patients with normal intraocular pressure (IOP). The only prospective published data are from patients from the Collaborative Normal Tension Glaucoma Study (CNTGS)[1], and such data are lacking for other types of glaucoma, which are even more common in clinical practice.

In addition to having great scientific interest, knowledge of the natural, untreated rate of glaucoma progression would have definite clinical importance, e.g., to allow estimates of the amount of damage created by delayed access to clinical care, or to decide upon test intervals for glaucoma screening or follow-up intervals for patients with suspect glaucoma. It would also be of value to know whether natural, untreated progression rates differ among groups of open angle glaucoma patients with different diagnoses.

The Early Manifest Glaucoma Trial (EMGT)[2] is a randomized clinical trial to evaluate the effectiveness of lowering intraocular pressure in open angle glaucoma. EMGT had an untreated control group and is the only such trial including patients with the most common clinical presentations of open angle glaucoma: 1. primary open angle glaucoma (POAG) with elevated IOP ("high tension" glaucoma – HTG; IOP≥21 mmHg) or 2. POAG with normal IOP ("normal tension" glaucoma – NTG; IOP <21 mmHg) and 3. pseudoexfoliative glaucoma (PEXG) .[2] The separation of POAG into HTG and NTG, using the traditional division of IOP at 21 mmHg, is historical and arbitrary, since IOP is a continuum. Furthermore, HTG and

NTG have the same signs and type of damage and today, POAG is considered a single disease[3]. Nevertheless, the concepts of HTG and NTG are widely used in clinical care, and POAG patients have different risks depending on IOP, with increasing IOP being associated with larger risks. Pseudoexfoliation syndrome is common and a large percentage of glaucoma patients in many parts of the world, e.g., Scandinavia, Finland, Greece, Russia, Turkey, India, parts of Africa and elsewhere, have PEXG.[4]

In EMGT half of patients were randomized to the untreated control group, therefore providing a unique database to study the natural history of glaucoma. Similar data on natural history are unlikely to become available, since several studies have demonstrated that IOP reduction is effective in glaucoma and ocular hypertension[5, 6, 7] This will make it difficult to follow cohorts of glaucoma patients without treatment in the future.

The aim of this paper is to report on one of the originally formulated study aims of EMGT [2] – to describe the natural history of the most common types of open angle glaucoma.

Material and methods

Design overview

The study design of EMGT (NIH ClinicalTrials. gov identifier NCT00000132. Date of registration: September 23, 1999) has been described in detail previously.[2] Briefly, EMGT included patients with newly diagnosed and untreated glaucoma with early to moderate damage. Most patients were identified in a large population-based screening of 44,000 citizens in Malmö and Helsingborg, Sweden, aged 50-80 years. The study was approved by the Ethics Committee of the University of Lund, Sweden, and the Committee in Research

Involving Human Subjects of the State University of New York at Stony Brook, and all patients provided written informed consent. Patients were randomized to treatment or to no treatment and followed at 3 month intervals. Treatment status was unchanged as long as definite progression did not occur. This progression outcome was defined as significant worsening, either because of reproducible visual field deterioration (detected through computerized visual field analysis, c.f. below), or increased cupping of the optic nerve head (detected by masked grading at a Disc Photography Reading Center.)

Data analysis

Patient groups

The current report includes those 118 patients (94%) who were followed for at least six years without treatment or progressed within 6 years, among 126 patients randomized to the untreated control group. For the present analysis, data were included only until the patient progressed, since treatment could be introduced at that time. Data were limited to 6 years of follow-up to achieve balance between having a sufficiently long duration of follow-up and an adequate sample size.

Analyses were based on eligible eyes for the trial. For the one-fifth of patients with two eligible eyes, the first eye to show progression was included in the analyses, or if no eye progressed, the eye with largest field defects at baseline (i.e., worse mean deviation values, cf. below).

The data analyses were performed for the full patient group, and for each of the three categories (HTG, NTG and PEXG). In EMGT, the median IOP among POAG patients was 21

mmHg. Therefore, the statistical comparison between HTG and NTG is based on a median split, as is the comparison between older and younger patients.

Assessment of visual field damage

In EMGT visual field testing was performed with the Humphrey Full Threshold algorithm using the 30-2 test point pattern. Fields were obtained every 3 months, unless the computerized analysis based on Glaucoma Change Probability Maps[8] indicated "tentative progression".[2] If so an extra field test was obtained after approximately one month to determine whether or not the eye had reached "definite progression".

In the current report the progression of visual field damage was analyzed in three different ways:

1. Rate of progression

We determined the rate of visual field progression in all study eyes. Here we used the mean deviation index (MD) [9, 10] to quantify the amount of visual field damage and the rate of progression. The MD index is used in several major glaucoma staging systems.[11, 12]
The rate of progression was expressed by the slope of a simple linear regression analysis of MD values over time. Since a normal eye has an MD ≈ 0 dB and a blind glaucoma eye has an MD value < ≈ -25-30 dB, depending on age, an eye would progress from normal to blind in about 25-30 years if the rate of progression was 1dB/year. With a more rapid progression rate of 2.5 dB/year an eye would go from normal to blind in 10-12 years.

Rates of progression were compared among the three diagnostic groups using analysis of variance (general linear model procedure in SAS).

2. Progression versus non-progression

The number of eyes meeting EMGT visual field progression criteria was calculated. EMGT progression criteria have been thoroughly described and analyzed.[2 13 14] Progression was determined using computer-assisted analyses in Glaucoma Change Probability Maps. [8] Each follow-up visual field was compared on a point-by-point basis to a baseline formed by the average of the last two baseline pre-randomization field tests. In the current study patients had undergone at least two visual field tests before the baseline field. If a point in a follow-up field showed a significant decrease of differential light sensitivity (at the $p < 0.05$ level), it was flagged as progressing. EMGT progression requires the occurrence of such decreased sensitivity in three consecutive tests at the same three or more test point locations, and is a sensitive and specific method to identify glaucomatous visual field worsening.[14] Proportions of progressed patients in the patient groups were compared with chi-square statistics.

3. Time to progression

Time to progression was calculated and displayed in Kaplan-Meier curves. Significance of differences was tested with the Log-Rank test**.**

Results

Baseline characteristics of all study patients and of those in each category are shown in Table 1. IOP was naturally higher in HTG than NTG patients, while IOP of PEXG patients was slightly lower than that of HTG patients. Patient age was similar among the three diagnostic groups. Attrition was minimal – only 4 patients were lost to follow-up, except for deaths.

1. Rate of progression

Table 2 presents both median and mean rates of progression, which followed the same pattern and differed markedly among the three diagnostic groups. Distributions were negatively skewed; therefore median rates were slower than mean rates, which were influenced by the extreme values. Median rates were: for the overall group (median: -0.40 dB/year), in HTG (-0.46 dB/year), NTG, (-0.22 dB/year), and PEXG (-1.13) (Table 2). The mean overall progression rate was -1.08 dB/year (SD ±2.07); in HTG it was -1.31 dB/year (SD ±1.93), in NTG it was about one-fourth of that, -0.36 dB/year (SD ±0.94), and in PEXG the mean progression rate was very fast -3.13 dB/year (SD ±3.69). These differences were statistically significant (NTG vs. HTG: $p=0.003$; PEXG vs. non-PEXG: $p<0.0001$) (Wilcoxon rank sum test).

There were very large variations among patients (Fig 1). A large percentage of patients showed low rates of progression, but a considerable minority progressed rapidly. As seen in Table 2, progression rates differed by age. They were significantly faster in older (median rate = -1.48 dB/year) than in younger (median rate = -0.60 dB/year) patients ($p=0.0002$; t-test), and the median progression rate in the 22 younger NTG patients was almost nil (Wilcoxon rank sum test).

2. Progression versus non-progression

By 6 years, 80 of the 118 eyes had shown glaucoma progression overall (68%). Progression was observed in 34/46 (74%) of HTG eyes, 32/57 (56%) of NTG eyes, and almost all of PEXG eyes, 14/15 (93%). Proportions differed significantly among groups ($p=0.01$) (chi-square test).

3. Time to progression

Median time to progression was 42.8 months for the total group. Time to progression differed significantly among diagnostic groups (Log-Rank test; $p<0.0001$) and was clearly shortest in PEXG and longer in HTG, and particularly in NTG. The large difference between diagnostic groups is clear from Fig. 2. Median times to progression were 19.5 months in PEXG, 44.8 months in HTG and 61.1 months in NTG.

Discussion

We studied the natural history of glaucomatous visual field progression in a large group of patients with open angle glaucoma, who had been randomized to no initial treatment in EMGT. After a follow-up time of 6 years, 80 of 118 (68%) had shown definite visual field progression. Progression rate and thus time to progression varied considerably among HTG, NTG and PEXG groups, and also among patients within each group. Rates of progression were considerably higher in patients with HTG than NTG and highest in patients with PEXG.

The NTG progression rates found by us are similar to those published in the only available paper on the subject.[1] Even if rates of progression have been unknown, except for NTG, the higher progression rate in HTG must be considered to be in line with other results, since the level of IOP has been shown to be an important factor for glaucoma progression [15 16 17] and for development of glaucoma.[6, 18, 19 20]

It is highly interesting that PEXG patients progressed so much more rapidly, and that the differences were highly significant despite the small sample size for PEXG, particularly

considering that the mean baseline IOP value was similar in the PEXG and HTG groups. Most ophthalmologists consider PEXG a more serious disease than HTG, but the explanation has almost always been that PEX glaucoma patients on the average have higher IOP values than POAG patients. The present analysis and our earlier analyses of risk factors for progression in all EMGT patients, treated as well as untreated, instead indicate that pseudoexfoliation is a strong factor for disease progression independent of IOP.[16, 17]

It is known that older age increases risk for development of glaucoma in patients with elevated IOP and for progression of glaucoma.[17, 19, 20] Nevertheless, the differences between rates of progression in younger and older patients for both HTG and NTG are quite striking. Further studies are needed to corroborate this finding.

The most important strength of the current report is that EMGT is the only prospective study with an untreated control group including the most common groups of OAG patients, and no on-going (or likely future) studies can provide the same data. The current natural history results are thus the first on POAG with elevated IOP (HTG) and on PEXG. POAG is by far the most common glaucoma diagnosis in clinical settings in Western countries, and PEXG is also a very common clinical diagnosis in many countries. Prospective natural history data have been published on NTG patients before, cf. above, but while NTG is common in population studies, these patients are often diagnosed late and are a minority in clinical glaucoma care, except in Japan, where NTG is particularly common.[21]

Other strengths are the prospective study format, and the fact that patients had perimetric experience prior to the study baseline, minimizing the perimetric learning[22-24] essential for proper definition of baseline damage. The frequent visual field testing, every 3 months, and

the long follow-up made it possible to calculate rate of progression with good accuracy. Patient recruitment, mainly through population screening, and excellent retention are additional strong points. Since patients, and not eyes, were randomized to the untreated control group analyzed here, there are also no confounding effects from treatment of the fellow eye.

The general applicability of our results to early and moderate glaucoma of the three types reported here should be at least moderately good. As mentioned above, the majority of patients were recruited through a population-based design. While patients with IOP values over 30 mmHg were ineligible, only 13% of all glaucoma patients had such screening pressures in at least one eye. The great majority of eligible patients agreed to participate. Almost all EMGT patients were of Caucasian origin, and the results may, therefore, not be, applicable to patients with non-European ethnicity.

One issue to consider is that for ethical reasons, all patients could not be followed without treatment after definite progression. We, therefore, do not know whether the natural history of visual field progression is linear also over very long periods of follow-up. Since there are indications that higher age[17, 19, 20, 25] and more damage[17] are risk factors for progression, one might instead argue that over long time periods the rate of progression ought to increase. Nevertheless, progression is usually linear in clinical settings, and several long-term studies have concluded that in such settings linear disease progression best fit the observed data.[26, 27]

Our results may be compared to those of the very few other studies on glaucoma natural history. The earlier study of natural history in normal-tension glaucoma patients (CNTGS) reported a mean progression of -0.39 dB/year[1], which is very similar to the mean progression

rate of -0.36 in our NTG group. Thirty-three percent of CNTGS patients showed progression, considerably less than in the present study, where 56% of NTG patients showed definite progression, but follow-up time was also considerably longer in the present study, and the percentage of progressed eyes of course increases with the length of follow-up. Also, time to progression of the patients with NTG in the current study was in line with that reported in CNTGS. Furthermore, the criteria for progression differed between CNTGS and EMGT. A 10-year follow-up study from St. Lucia reported increases in visual loss among 205 black individuals with manifest or suspect glaucoma, who had remained untreated after being detected in a 1986-7 survey.[28] Less data are available for these patients than in our prospectively followed cohort, and field results are reported in a different way using so-called AGIS scores[29]. Recently, untreated mean rates of progression have been estimated from cross-sectional data. These means, although not reporting data for HTG, NTG and PEXG separately, are of the same magnitude as the overall mean result in the current study.[30]

A striking feature of the results is the large inter-patient variability in rate of progression, not only among, but also within the diagnostic groups. Thus individual progression rates cannot be predicted, but must be determined with repeated visual field testing. We found that glaucoma in a clear majority of patients progressed during the follow-up time, based on our criteria. Additional patients must have had worsening glaucoma, but not enough to meet these progression criteria. While the latter criteria are strict, not much deterioration is needed in most patients to ascertain definite progression; the average change of MD associated with progression was -1.83 dB in an earlier study involving the whole EMGT cohort [13], and EMGT criteria have been shown to be more sensitive than criteria used in two other large glaucoma trials comparing various modalities of treatment.[14]

Population screening for undetected open angle glaucoma is now seriously considered, and our results are very relevant for those 50% or more of glaucoma patients that are undiagnosed in the Western world.[31-38] The present results also provide new, clinically important and relevant information. Many of these untreated EMGT patients progressed only slowly, and the median progression rate of the total patient group corresponds to progressing from a full field to blindness in approximately 70 years. Nevertheless, a substantial minority progressed much more rapidly, and the mean progression rate seems more alarming, corresponding to going from a full field to blindness in approximately 25 years. With that rate, and if the diagnosis is made when half the visual field is already gone, the time to blindness would be merely a dozen years. We feel that the large difference between median and mean rates makes it important to report both; the median rates are suitable for demonstrating differences between groups, while the means and not the medians give an estimate of the total loss of visual function over time in the patient cohort. The average NTG patient lost visual function rather slowly, at a quarter of the speed of average patients with HTG when mean progression rates are compared, and at half of the speed if medians are considered. Untreated PEXG progressed fast, even with rather low IOP values. This is of importance when protocols for glaucoma screening or case-finding are devised. Our findings might be used as an argument to justify use of broad-scale tonometry to identify individuals who might need glaucoma treatment. The rapid deterioration in PEXG suggests that it may be advisable to always look for signs of PEXG in screening and glaucoma case finding. The results of the current study also provide a new and much needed benchmark to assess the success, or lack of success, of different treatment modalities for glaucoma.

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