Risk of Glaucoma in Ocular Hypertension with and without Pseudoexfoliation

Kirsti Grødum, MD, PhD, Anders Heijl, MD, PhD, Bo Bengtsson, MD, PhD

Purpose: To compare glaucoma conversion rates in patients with ocular hypertension (OH) with and without pseudoexfoliation.

Design: Cohort study, based on 32 918 screening participants.

Participants and Controls: Ninety-eight patients with OH and pseudoexfoliation and 98 matched controls.

Main Outcome Measure: Perimetric glaucoma conversion.

Methods: A population-based glaucoma screening of elderly citizens of Malmö, Sweden, was conducted between 1992 and 1997 to recruit participants for the Early Manifest Glaucoma Trial. Screening participants with intraocular pressure (IOP) between 24 and 32 mmHg and pseudoexfoliation were compared to controls among other screening participants without pseudoexfoliation but matched for baseline IOP, age, and gender, and the 2 groups were invited to a reexamination. Computerized visual field tests were performed to identify persons with manifest glaucoma. Visual acuity, refraction, IOP, and central corneal thickness were also measured.

Results: After a mean of 8.7 years (range: 6.3–11.4), 54 of 98 patients (55.1%) with pseudoexfoliation at the baseline examination and 27 of 98 patients (27.6%) without pseudoexfoliation had developed glaucoma. The risk ratio was 2.0 ($P<0.0001$).

Conclusion: The glaucoma conversion rate was twice as high in patients with OH and pseudoexfoliation as in control patients matched for IOP, age, and gender. Thus, pseudoexfoliation was a strong independent risk factor for glaucoma in patients with OH. *Ophthalmology 2005;112:386–390 © 2005 by the American Academy of Ophthalmology.*

The results of the Ocular Hypertension Treatment Study (OHTS) show that treatment can prevent or delay the development of glaucoma in patients with ocular hypertension (OH).[1] However, several studies indicate that a majority of patients with untreated OH do not develop glaucoma even after long follow-up.[2–5] Considering the potential side effects of pressure-lowering treatment,[6,7] including cataract formation,[8] and the difficulties often associated with termination of therapy, once initiated, it seems clear that not all patients with OH should be given prophylactic treatment.[9,10] Indeed, the OHTS's authors conclude that their results do not imply that all patients with ocular hypertension should receive treatment, but that clinicians should consider treatment for individuals with ocular hypertension who are at moderate or high risk for developing glaucoma.[1] Identifying these is therefore an important task.[11]

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From the Department of Ophthalmology, Malmö University Hospital, University of Lund, Malmö, Sweden.

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Correspondence and reprint requests to Kirsti Grødum, MD, PhD, Department of Ophthalmology, Malmö University Hospital, S-20502 Malmö, Sweden. E-mail: kirsti.grodum@oftal.mas.lu.se.

Pseudoexfoliation glaucoma has sometimes been referred to as a rare secondary glaucoma, mainly seen in Scandinavian countries, but is now understood to be occurring worldwide. However, there may still be a need to increase the awareness of its importance.[12] The influence of pseudoexfoliation on the prognosis of ocular hypertension is an important issue, considering recent results regarding the benefits of pressure-lowering treatment (e.g., from the OHTS[1] and the Early Manifest Glaucoma Trial[8]).

Previous studies have demonstrated that the prevalence of glaucoma is higher in patients with pseudoexfoliation than in those without pseudoexfoliation.[13–15] Pseudoexfoliation is also believed to be an important independent risk factor in patients with ocular hypertension.[15–17] Høvding and Aasved reexamined patients diagnosed with ocular hypertension at a previous mass screening[18] and found pseudoexfoliation to be an important risk factor, but the number of patients with pseudoexfoliation was small (n = 13.) Pohjanpelto reported a high incidence of glaucoma in patients with ocular hypertension and pseudoexfoliation,[19] but the study was clinic based, with a 10-year mean age difference between ocular hypertensive patients with pseudoexfoliation and those without. In a study by Brooks and Gillies, about one quarter of 153 patients with ocular hypertension and pseudoexfoliation developed glaucoma during a mean follow-up period of 6 years,[20] but the study was based on referred patients, and there was no control group. Results from a larger adequately controlled population-based study would therefore be valuable.

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Our aim was to study the effect of pseudoexfoliation on the risk of developing glaucoma in persons with ocular hypertension, identified in the large mass screening for glaucoma conducted in Malmö in connection with the Early Manifest Glaucoma Trial (EMGT).

Materials and Methods

To recruit participants for the EMGT, a population-based glaucoma screening of elderly citizens of Malmö, Sweden was conducted between 1992 and 1997.[12] A total of 32 918 citizens attended this screening at Malmö University Hospital. This corresponded to 77.5% of the invited population, comprising men born between 1918 and 1932 and women born between 1918 and 1939. Citizens who had visited the eye department at Malmö University Hospital in the preceding year were not invited (n = 4117).

At the initial screening examination, visual acuity (VA), refraction, and intraocular pressure (IOP) were measured. If the IOP was above 20 mmHg in at least one eye, slit-lamp examination of the anterior segment with dilated pupils was performed, the objective being to detect pseudoexfoliation. Optic disc photographs were taken and evaluated for signs of glaucomatous damage (i.e., saucerization, marginal cupping, notches, vertical elongation of the cup, narrow rims, large cups in small discs, localized nerve fiber defects, or optic disc hemorrhages). If such signs were present in the photographs, or if IOP was higher than 25 mmHg, participants were called back for a complete eye examination, including computerized visual field (VF) tests with the Humphrey Full Threshold 24-2 program, using the Glaucoma Hemifield Test[21,22] to determine if they had manifest glaucoma damage. This was defined as the presence of repeatable VF defects compatible with glaucoma and not explained by other ocular or neurological causes. Thus, the definition of glaucoma was in principle based on the same criteria as the EMGT VF eligibility criteria.[23]

At baseline, all patients included in the present study were untreated, and all had normal VFs and/or optic disc photographs that were considered to be without any signs of glaucoma.

All screening participants with an IOP of ≥24 mmHg at baseline were identified. Those with an IOP of ≥32 (n = 29) were excluded, partly to facilitate comparison with the OHTS[8] and partly because most physicians would begin treatment at this IOP level even in the absence of documented damage. A total of 864 (2.7%) glaucoma-negative screening participants had IOP between 24 and 32 mmHg. Among these, 153 (17.7%) had pseudoexfoliation at the baseline examination between 1992 and 1997. Twenty-seven of them were deceased, and 11 had moved out of the region. Thus, 115 individuals with ocular hypertension and pseudoexfoliation remained. Controls matched for IOP, age, and gender were identified among the remaining screening participants with IOP between 24 and 32, but without pseudoexfoliation (Fig 1). Ninety-eight of 115 matched pairs completed the reexamination. Screening participants had been examined in a consecutive fashion according to date of birth, resulting in very similar follow-up times in participants with pseudoexfoliation and controls. Participants were included in the study in matched pairs. If the participant with pseudoexfoliation was unable or unwilling to participate, the control patient in question was excluded. If the original matched control was unable or unwilling to participate, up to 3 new controls were invited before excluding the corresponding study patient with pseudoexfoliation. The 2 groups (participants with OH and pseudoexfoliation and controls with ocular hypertension without pseudoexfoliation) were then invited to a reexamination.

At the reexamination, VA, refraction, and IOP were measured. The reexamination also included a computerized VF test with the Humphrey 24-2 program and pachymetry (i.e., measurements of central corneal thickness [CCT]).

The glaucoma diagnosis at the reexamination was based on reproducible VF defects with the Glaucoma Hemifield Test outside normal limits on 2 consecutive visits within a 3-month period. The defects would have to be compatible with glaucoma and not explainable by other ocular or neurological conditions. If the first test was within normal limits in both eyes, the participant was considered glaucoma negative, and the procedure was not repeated.

The participants included in this study were between 57 and 76 years of age at the initial glaucoma screening between 1992 and 1997. At the reexamination, they were on average 8.7 years older, with a mean age of 77 years. This fact implies that strict adherence to the diagnostic criteria was not always possible. Thus, 18 of the 81 newly diagnosed glaucoma patients (22.2%) did not complete 2 VF tests within 3 months. Among these, 6 patients completed only one VF test within the designated 3-month period, but had previous series of well-documented VF defects compatible with manifest glaucoma. Five patients completed only one VF test, but had corresponding obvious optic nerve head damage. Four patients were unable to participate in any VF testing in the designated 3-month period, but had obvious glaucomatous damage in the optic disc photograph taken at the reexamination, in addition to previously documented defects with computerized VF tests. In 3 patients, the diagnosis was based solely on existing medical

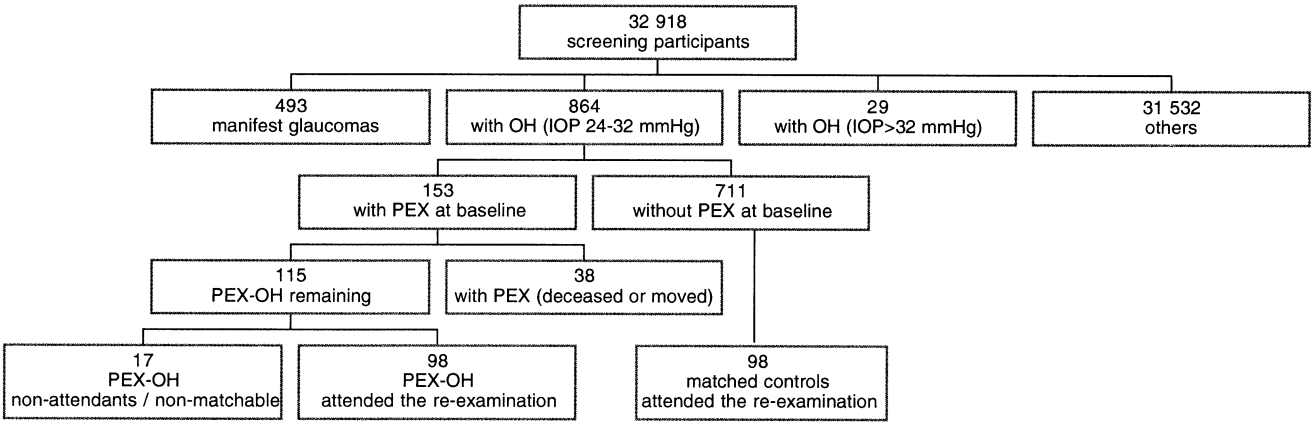

Figure 1. Recruitment of patients. IOP = intraocular pressure; OH = ocular hypertension; PEX = pseudoexfoliation.