European Journal of Ophthalmology / Vol. 11 no. 3, 2001 / pp. 245-251

Changes in visual acuity and refraction in the exfoliation syndrome. A five-year follow-up study

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PURPOSE. *To examine changes in visual acuity (VA) and refraction in non-glaucomatous patients with unilateral exfoliation syndrome (EXS).*

METHODS. *The best corrected values for VA (Snellen acuity cards) subjectively adjusted for refraction, and IOP were measured, and the development of lens opacities was examined in 46 non-glaucomatous patients with unilateral EXS.*

RESULTS. *After five years the rate of conversion to bilateral exfoliation was 22% and to exfoliative glaucoma 30%. There was a significant decrease in VA in the exfoliative (E) eyes (median; QI, QIII, range: 1; 0.8, 1, 0.4-1.3 vs. 0.55; 0.4, 1, 0.05-1.4, p<0.0001) and the fellow, initially non-exfoliative (NE), eyes (1; 0.9, 1, 0.3-1.3 vs. 0.7; 0.5, 0.9, 0.1-1.4, p<0.0001) and a significant myopic change in refraction in the E eyes (+1.02 ± 2.48 vs. +0.11 ± 3.06, p=0.0001) and the NE eyes (+0.99 ± 2.25 vs. +0.43 ± 2.55 D, p<0.01). At study entry the difference in refraction between the fellow eyes (refraction in the NE eye – refraction in the E eye) was -0.27 ± 1.00D. After five years it was +0.32 ± 1.44 (p 0.016), reflecting greater myopic changes in the E eyes. The main type of lens opacification was nuclear sclerosis.*

CONCLUSIONS. *In five years, significant decreases in VA and myopic shifts in refraction occurred in the E and fellow eyes. The E eyes showed significantly greater myopic changes than the fellow eyes; the cause was clearly nuclear sclerosis, which must be taken into account in the long-term management of patients with EXS. (Eur J Ophthalmol 2001; 11: 245-51)*

KEY WORDS. *Unilateral exfoliation syndrome, Exfoliative glaucoma, Visual acuity, Refraction, Lens opacification, Nuclear sclerosis*

Accepted: December 11, 2000

INTRODUCTION

Despite the survival of the popular notion that a true myopic shift in refraction results from a slow increase in the refractive power of the lens, recent cross-sectional (1-4) and longitudinal (4-6) population-based studies have shown that myopic shifts in refraction occur only in patients in their 20's, 30's and 40's. Increasing hyperopia is observed in patients in their 60's and 70's. After the age of 70 years, a hyperopic or a myopic shift may be seen (1, 4). There have been no such cross-sectional or longitudinal studies in eyes with the exfoliation syndrome (EXS).

Increased lens opacification is thought to be associated with EXS and exfoliative glaucoma (7-12). As nuclear sclerosis is the most frequent type of cataract in EXS (13, 14) and as myopia increases with nuclear sclerosis (15, 16), we prospectively followed longitudinal changes in refraction and visual acuity (VA) in patients with EXS. To find out whether there were any differences in refraction or VA between the exfoliative (E) and fellow non-exfoliative (NE) eyes, we selected patients with unilateral EXS for this five-year follow-up study.

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MATERIALS AND METHODS

Sixty-three non-glaucomatous, non-diabetic subjects (mean age 69.2 ± 6.6 years, range 45-87 years) with unilateral EXS were examined for VA, refraction, IOP, biomicroscopy, lens opacities and fundus changes (17). The study included no eyes previously subjected to ocular surgery or with corneal opacities, ocular trauma, signs of intraocular inflammation or macular degeneration affecting vision. The patients were examined on average once a year (Tab. I).

After five years, 46 of these subjects (mean age at study entry 67.0 ± 6.4 years, range 45-83 years) were available for follow-up examination (Fig. 1). Seventeen were not available: 7 had died and 10 were unable or unwilling to participate in the study. Case histories of 14 of these 17 patients were examined for the presence of exfoliation and glaucoma, and for cataract extractions. Information from case reports was used when calculating conversion rates to bilateral disease and to glaucoma and when counting the number of cataract extractions. Three patients who had died within 1-2 years of the first examination were excluded.

Thirty-three subjects (mean age 72.4 ± 6.0, 50-86 years) still showed clinically unilateral disease (Tab. I). Of these, 22 had no glaucoma in either eye. Eleven patients had glaucoma either in the E eye (9 patients) or in both eyes (2 patients). Nine patients used timolol maleate, one betaxolol, one dipivefrin and only two used pilocarpine in the E eye. The NE eyes were treated with timolol maleate. Argon laser trabeculoplasty (ALT) had been done in three E eyes. No filtering operations had been done. Thirteen patients (mean age 72.0 ± 7.5, 60-88 years) had converted to bilateral exfoliation (Tab. I), of whom 7 had no glaucoma in either eye but 6 had glaucoma either in the E eye (2 patients) or in both eyes (4 patients). Four patients used timolol maleate in both eyes, one patient had betaxolol in the E eye and one dipivefrin in both eyes. Only two patients used pilocarpine in both eyes. ALT had been done in two E eyes and one fellow eye. No filtering operations had been done.

TABLE I - PATIENTS WITH EXS AT STUDY ENTRY AND FIVE YEARS LATER

Study entry: Unilateral exfoliation syndrome, no glaucoma in either eye	**63**
Died	7
Not available for follow-up	10
(Case histories of 14 patients examined)	
End of study, after five years:	**46**
Unilateral exfoliation	**33**
No glaucoma	22
Glaucoma only in the exfoliative eye	9
in both eyes	2
Bilateral exfoliation	**13**
No glaucoma	7
Glaucoma only in the exfoliative eye	2
in both eyes	4

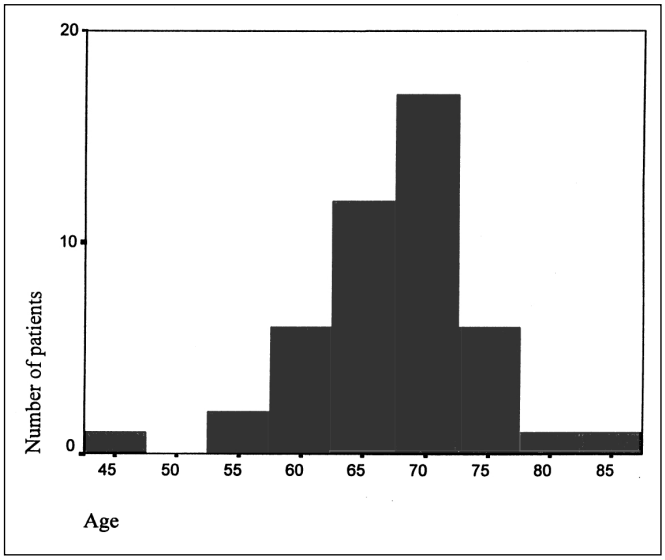

Fig. 1 - *Age distribution at study entry.*

Clinically, unilateral exfoliation was defined as biomicroscopically detectable exfoliation material on the anterior surfce of the lens capsule or at the pupillary border in the E eye only after pupillary dilatation with 10% phenylephrine hydrochloride. Nuclear sclerosis implies hardening of the lens nucleus. The grading was done by the senior author only, in an open fashion, in a dark room using a Haag-Streit slit lamp with 45 degrees slit angle. The score was arbitrarily from one to three plus, in which grade two plus met the criteria for nuclear sclerosis. Similarly, the cortical wedges from degradation of cortical lens fibers were classified as cortical opacities, and two plus subcapsular opacity met the criteria for a subcapsular cataract.

Refraction was measured with the Welch Allyn retinoscope. The examiner was not aware of which

eye had exfoliation. The best corrected VA was measured with subjectively adjusted refraction values at 5 meters, using Snellen acuity cards. No autorefractor or cycloplegics were used. For analysis, the power of the cylinders was converted into its spherical equivalent. The eye was defined as emmetropic when its refraction was between –0.5 D ≥ and ≤ +0.5 D, hyperopic when it was > +0.5 D and myopic when it was < -0.5 D. For a change in refraction, a decrease of < -0.5 D or an increase of ≥ +0.5 D was required. Biomicroscopy of the anterior segment and ophthalmoscopy using a 90-diopter Volk lens (Volk Optical, Mentor, OH) were done after dilatation of the pupils. The IOP was measured using the same Goldmann applanation tonometer with a Haag-Streit slit lamp. All measurements were done by the same senior author. Glaucoma was defined as IOP > 21 mmHg with typical glaucomatous visual field and/or optic disc changes. Visual fields were tested with the automated Octopus G1 program.

Statistical methods

The Wilcoxon signed-rank test and the t-test for paired samples were used to compare differences between the fellow eyes and to analyse changes with time. The t-test for independent series was used when comparing age differences between groups. Pearson's chisquare two-sided test and Fisher's exact test were used for proportions. P<0.05 was selected to denote statistical significance of differences.

All patients gave their informed consent to inclusion in the study, which was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

RESULTS

During the follow-up period the rate of conversion to bilateral exfoliation was 22% (13/60), 30% to exfoliative glaucoma (18/60) (in eyes that were already exfoliative at the start), and 7% to primary open-angle glaucoma (POAG) (4/60).

Visual acuity

Pre-operative VA and refraction values were used for the eyes that had undergone cataract extraction during the follow-up period.

The median VA of 1.0 at the beginning (median; QI, QIII, range: 1; 0.8, 1, 0.4-1.3) fell to 0.55 at the end (0.55; 0.4, 1, 0.05-1.4, p<0.0001) in the E eyes. A similar change took place in the fellow eyes (1; 0.9, 1, 0.3-1.3 vs. 0.7; 0.5, 0.9 0.1-1.4, p<0.0001) during the follow-up period. In pairwise analyses the fellow eyes did not differ in VA at the start or after five years.

There was a decline in VA of ≥ 2 Snellen lines in 54% of the E and fellow eyes. Patients with a decline in VA of ≥ 2 Snellen lines in the E eyes (69.8 ± 5.2 vs. 65.0 ± 6.8 years, p<0.01) or in the NE eyes (70.3 ± 5.2 vs. 64.4 ± 6.4 years, p<0.001) were significantly older than those with no such change. The cause, in 76% of the E eyes and 72% of the NE eyes, was more pronounced lens opacification. Macular degeneration contributed to the decline in VA in 4% of the E and 4% of the NE eyes. The cause was both lens opacification and macular degeneration in 20% of the E eyes and 20% of the NE eyes. In one NE eye the cause was lens opacification and corneal guttata changes.

At study entry, biomicroscopy revealed nuclear sclerosis in 46% of the E and 41% of the NE eyes. The cor-

TABLE II - THE FREQUENCIES OF NUCLEAR, CORTICAL, SUBCAPSULAR AND MIXED CATARACT IN THE PAIRED EYES AT STUDY ENTRY AND AFTER FIVE YEARS

	Study entry exfoliative eye (%)	Fellow eye (%)	End of study exfoliative eye (%)	Follow eye (%)
Nuclear sclerosis	46	41	85	83
Cortical	14	10	19	13
Subcapsular	8	2	9	4
Mixed	19	11	23	13

responding figures for cortical cataract were 14% and 10%, for subcapsular cataract 8% and 2% and for mixed cataract 19% and 11%. After 5 years, nuclear sclerosis was found in 85% of the E and 83% of the fellow eyes. The corresponding figures for cortical cataract were 19% and 13%, for subcapsular cataract 9% and 4% and for mixed cataract 23% and 13% (Tab. II).

Refraction

During the follow-up there was a significant change in refraction in the E eyes (+1.02 ± 2.48 vs. +0.11 ± 3.06, p=0.0001) (Fig. 2) and the NE eyes (+0.99 ± 2.25 vs. +0.43 ± 2.55 D, p<0.01) (Fig. 3). At study entry the difference in refraction between the fellow eyes, calculated as refraction in the NE eye minus refraction in the E eye, was –0.27 ± 1.00 D. After five years the difference was +0.32 ± 1.44 (P 0.016) reflecting higher myopic changes in the E eyes (Fig. 4 and Fig. 5). The result did not change when the patients using pilocarpine were excluded from the analysis.

At the start, 72% of the E eyes and 72% of the NE eyes were hyperopic, 17% and 15% were myopic and 11% and 13% were emmetropic. After five years the figures for hyperopia were 52% and 52%, for myopia 35% and 20% and for emmetropia 13% and 28%.

During the study period the change in refraction was myopic in 46% of the E (age 69.0 ± 4.6 years) and 50% of the NE (age 70.4 ± 5.3 years) eyes, and hyperopic in 4% of the E (age 70.0 ± 2.8 years) and 9% of the NE (age 65.0 ± 7.1 years) eyes. No change in refraction occurred in 50% of the E eyes (age 66.2 ± 7.8 years) and 41% of the NE eyes (age 64.8 ± 6.4 years). The NE eyes with a myopic shift in refraction were significantly older than those with no change (p < 0.01). This pattern was not found in the E eyes.

Cataract extraction

Seven patients had undergone cataract extraction in the E eye, three in the NE eye and three in both eyes. As there are uniform indications for cataract surgery in our hospital it can be noted that the E eyes needed surgery more often. Among the three who were operated on both eyes, the E eye was operated first.

IOP

The E eyes had higher IOP than the fellow eyes both at the start (17.4 ± 3.0 vs. 15.4 ± 2.4 mmHg, p<0.0001) and after five years (17.7 ± 3.7 vs. 15.2 ± 3.5 mmHg, p<0.001). However, the changes in IOP in the E and the fellow eyes during the follow-up were not significant.

DISCUSSION

Of 63 non-glaucomatous patients with unilateral EXS selected for the present five-year follow-up study, 46 were available for examination of the changes in VA and refraction in the E and the fellow eyes. The non-glaucomatous and non-exofoliative fellow eyes served as controls. Any effects of age, sex, environment, systemic diseases and systemic medication were ruled out by comparing the fellow eyes.

There is disagreement as to whether EXS is ever unilateral or merely manifests asymmetrically (18). Immunohistochemical studies have indicated that, in unilateral cases, there is a similar microangiopathy of the anterior uvea in the E eyes and the fellow eyes (18). However, even with a long follow-up time, a number of patients continue to show exfoliation deposits in one eye only. Hence the term clinically unilateral EXS has been adopted.

Thirty percent of the eyes had developed bilateral exfoliation. In earlier studies, conversion rates of 14-41% in five years have been reported (19, 20). Exfoliation glaucoma was diagnosed and glaucoma medication was started in 30% of the E eyes. POAG was diagnosed in 7% of the NE eyes during the study period. These eyes presented early glaucoma, which obviously had no effect on VA.

There was a decline in VA of ≥2 Snellen lines in 54% of the E and NE eyes and these patients were older than those with no such decline. The decline in VA was due to lens opacification alone in 76% of the E eyes and 72% of the NE eyes, and combined with macular changes in 96% and 92%. Previous reports have also found a decline in VA with age, and an association between senile cataract and age (21). In large population-based studies, age and female sex were independent predictors of visual impairment (22, 23). The chief causes of visual loss were age-related mac-

ular degeneration and cataract (21, 22), as in this study.

In earlier population-based studies the prevalence rates for hyperopia varied from 22.1% (43-54 years) to 68.5% (>75 years), for myopia from 43% (43-54 years) to 14.4% (>75 years) and of emmetropia from 12.7% to 57.1% (1,5), depending on definitions and on the composition and age of the population studied. In age-adjusted calculations, hyperopia was more frequent than myopia (49.0% vs. 26.2%) (3) and a significant relationship was observed between level of education and refractive error, the prevalence of myopia rose with the educational level) (3, 24). The prevalence of hyperopia (72-52%) decreased and that of myopia (15-35%) increased in this study.

Recent cross-sectional (1-4) and longitudinal (4-6) population-based studies have shown a myopic shift

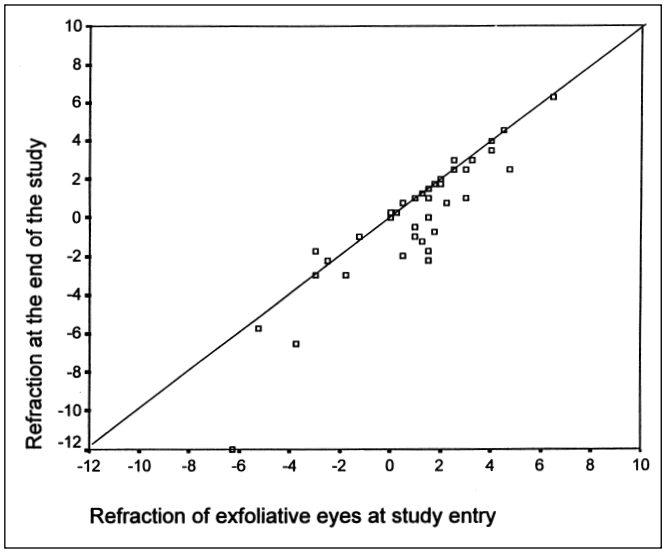

Fig. 2 - *Refraction of the exfoliative eyes at study entry and after five years.*

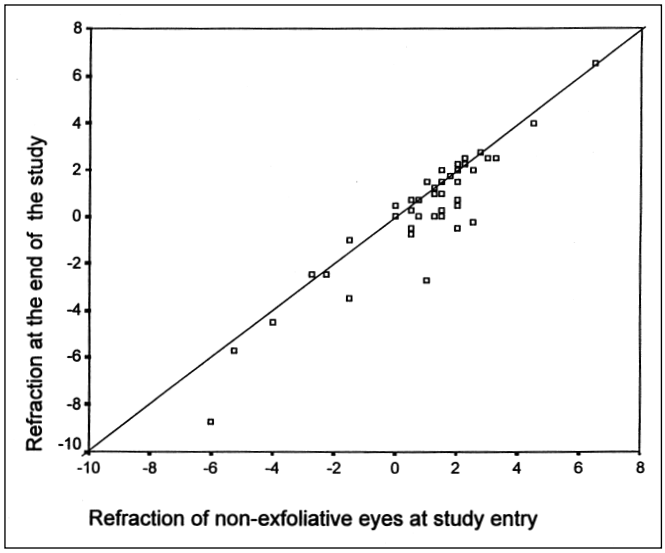

Fig. 3 - *Refraction of the fellow, initially non-exfoliative eyes at study entry and after five years.*

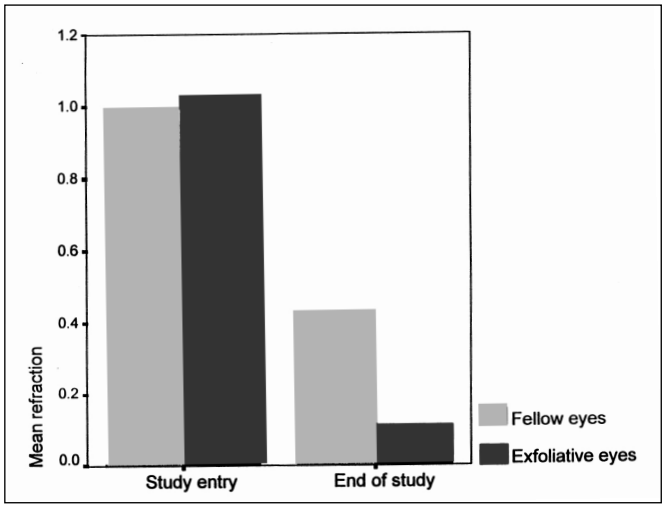

Fig. 4 - *During the follow-up period there was a significant change in refraction in the E eyes (+1.02 ± 2.48 vs. +0.11 ± 3.06, p=0.0001) and the NE eyes (+0.99 ± 2.25 vs. +0.43 ± 2.55 D, p<0.01).*

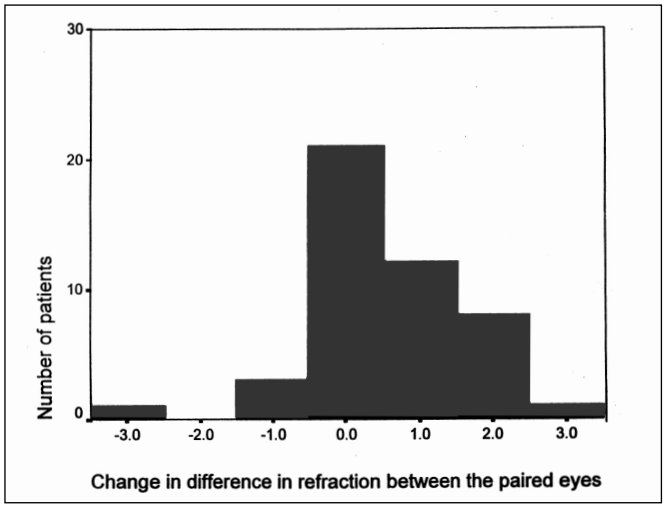

Fig. 5 - *At study entry the difference in refraction between the fellow eyes, calculated as refraction in the NE eye – refraction in the E eye, was –0.27 ± 1.00 D. After five years the difference was +0.32 ± 1.44 (p 0.016), reflecting stronger myopic changes in the E eyes. The distribution of that change is shown as the difference in refraction between the paired eyes.*

in refraction among patients in their 20's – 40's, and increasing hyperopia among patients in their 60's and 70's. After the age of 70 years, either a hyperopic or a myopic shift was observed (1, 4). In the present study, in which 46% of the patients were ≥ 70 years of age at the start and 74% were ≥ 70 years after five years, a myopic change in refraction had occurred in 50% of the E and 46% of the fellow eyes. The change was hyperopic in only 4% of the E eyes and 9% of the fellow eyes. The patients with a myopic shift in refraction in the NE eyes were significantly older (mean age 70.4 years) than those with no change in refraction (mean age 64.8 years). The E eyes, in which the myopic change in refraction during the study period was more pronounced than in the fellow NE eyes, behaved in a different way and no such age differences could be detected between the eyes showing myopic, hyperopic or no change in refraction.

It has to be emphasized that in our study the examiner was not aware of which of the patient's eyes had exfolation. The myopic change in refraction in the paired eyes, and especially in the E eyes, reflected cataractous changes in the lenses. The cause of the myopization was clearly nuclear sclerosis (15, 16), for pilocarpine was used in only four E eyes and two fellow eyes (25-27) and timolol maleate is not known to be cataractogenic (28, 29). Myopia increases with nuclear sclerosis and posterior subcapsular cataract (15, 16), but hypermetropization is associated with cortical cataract (15). In clinical and histopathological studies, the predominant type of cataract in EXS is nuclear sclerosis, with cortical and supranuclear cataracts less common and severe (13, 14, 17). This was confirmed by our data. In a Finnish cross-sectional population-based study, stepwise logistic regression analysis showed the only risk factor for cortical cataract was age and the risk factors for nuclear sclerosis were age and exfoliation (30). The prevalence of nuclear opacities increased from 46% to 85% in the E and from 41% to 83% in the fellow eyes during follow-up. The change was more rapid for nuclear sclerosis than for cortical or subcapsular opacities. In an earlier study, nuclear sclerosis also changed much faster than cortical or posterior subcapsular opacities (31).

In five years, significant changes in VA and refraction occurred in the E and fellow eyes. In half the patients the change was myopic in both eyes. These myopic changes reflected cataractous changes in the lenses and the cause was clearly nuclear sclerosis. The E eyes showed significantly stronger myopic changes than the fellow eyes and thus apparently confirmed that EXS is a risk factor for lens opacification and especially for nuclear sclerosis.

ACKNOWLEDGEMENTS

The authors are greatly indebted to Timo Pessi, M.Sc., statistician at the Department of Computer Services in Helsinki University Hospital, for his assistance with the statistics.

This study was supported by a grant from the Paulo Säätiö (the Paulo Foundation), the Silmäsäätiö (the Finnish Eye Foundation) and the Silmä-ja Kudospankkisäätiö (the Finnish Eye and Tissue Bank Foundation).

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