Editorial

Solving the enigma of exfoliation glaucoma: a breakthrough in glaucoma research

Acta Ophthalmol. Scand. 2007: 85: 808–809

doi: 10.1111/j.1600-0420.2007.01103.x

Exfoliation syndrome (XFS) is an age-related disorder common in many populations although there are also considerable ethnic and geographical differences (Ringvold 1999). XFS is characterized by the accumulation of abnormal microfibrillar deposits that line the aqueous bathed surfaces of the anterior segment of the eye; this may lead to elevated intraocular pressure (IOP) and exfoliation glaucoma (XFG), the latter being characterized by rapid progression, high resistance to medical therapy and worse prognosis than primary open-angle glaucoma (Schlotzer-Schrehardt & Naumann 2006). This condition was first reported by the Finnish ophthalmologist Lindberg in his doctoral theses in 1917, some 90 years ago. An English version was published in this journal in 1989 (Lindberg 1989). A recent study found 15-year risk of XFS conversion to XFG to be about 60% (Jeng et al. 2007).

XFS and XFG are common in the Nordic countries with the exception of Denmark: this has generated a considerable interest among Nordic ophthalmologists and is reflected in their journal, including the present issue.

Åström et al. (2007), in northern Sweden, present a remarkable population-based study in a single municipality on 339 persons aged 66 years and find the prevalence of XFS to be 23%. A follow-up study at 7-year intervals over 21 years finds the prevalence of XFS by 87 years of age to have risen to 61%, an annual incidence of 1.81%. Over the same time, the prevalence of open-angle glaucoma rose from 2.1% at 66 years to 25% at 87 years, with XFG accounting for 59% of glaucoma cases in the latter group.

Arnarsson et al. (2007), of Reykjavik, Iceland, find the prevalence of XFS in the Reykjavik Eye Study (RES) to be 11% for those aged ≥50 years. The RES includes a random sample from the population census, equal percentage for each year of birth and both sexes – altogether 1045 persons. They also examined other ophthalmic variables commonly associated with XFS such as central corneal thickness, IOP, cataract and anterior chamber depth. The RES has a lower prevalence of XFS for 66 year olds than the Swedish study, namely 9.6% versus 23%.

In Reykjavik, the prevalence of XFS for persons aged ≥80 years is 41% and in the Swedish study it is 61% for 87 year olds. Both studies find women to be more commonly affected than men after adjusting for age. Considering open-angle glaucoma, the prevalence is similar for both studies for those 66 years of age. In the RES, glaucoma is three times more common in XFS eyes than in non-XFS eyes (Jonasson et al. 2003); the Swedish study finds XFS to increase the risk of open-angle glaucoma fourfold.

Arnarsson et al. find mean IOP to be elevated in eyes with XFS compared to those with no XFS; they did not, however, find significant difference between eyes with XFS and eyes without XFS regarding central corneal thickness, nuclear cataract, lens thickness and anterior chamber depth after controlling for age and gender. Previous reports regarding these parameters have not been conclusive. Arnarsson et al. emphasize the importance of random sampling from the population and of adjusting for age and gender. Although their study is among the largest addressing these issues, they also acknowledge that they are not in all instances able to resolve all these issues conclusively.

Tarkkanen et al. (2007), from Finland, address the frequency of systemic vascular disease in patients with primary open-angle glaucoma and exfoliation glaucoma. Abnormal fibrils can be identified in patients with XFS by electron microscopy in the heart, lung, liver, kidney and other tissues; this has created interest in possible clinical consequences. The authors compare 344 persons with primary open-angle glaucoma and 155 persons with exfoliation glaucoma with respect to systemic disease including arterial hypertension, ischaemic heart disease and diabetes mellitus, the last being a known modifier of risk for cardiovascular disease. They do not find different frequency of arterial hypertension or ischaemic heart disease among patients with exfoliation glaucoma compared to the control group in their comprehensive study, which is in agreement with some other major studies and contradicts some cited in

their article. The study by Tarkkanen et al. examining the whole population does, however, seem to be more comprehensive than most studies and may be more likely to give conclusive answers.

Recently, an Icelandic group of scientists (Thorleifsson et al. 2007) identified two risk variants in the lysyl oxidase-like 1(*LOXL1*) gene (15q24.1) associated with exfoliation glaucoma. Collaborating with Swedish scientists, they replicated the results in a Swedish population. *LOXL1* is one of many enzymes that are essential for the formation of elastin fibres; the *LOXL1* gene plays a role in modifying tropoelastin, the basic building block of elastin and catalyses the process from monomers to cross-link and form elastin. A person homozygous for both of the highest risk haplotypes was 700 times more likely than those homozygous for the low-risk variants to have XFG. Thorleifsson et al. (2007) appear to explain the genetic aetiology of exfoliation glaucoma in virtually all instances. In Iceland and Sweden, the high-risk haplotype is very common with a frequency that averages about 50% in the general population; approximately 25% are homozygous (two copies) for the haplotype with the highest risk.

After many years of slow, incremental progress in our understanding of XFS and XFG, this paper on underlying genetics in this complex disorder presents a breakthrough in exfoliation research. This may be the first step, and a very important one, towards developing a new medical therapy designed to deal with the underlying aetiology rather than the clinical consequences of exfoliation glaucoma.

Fridbert Jonasson

References

Arnarsson A, Damji KF, Sverrisson T, Sasaki H & Jonasson F (2007): Pseudoexfoliation in the Reykjavik Eye Study: prevalence and related ophthalmological variables. Acta Ophthalmol Scand **85**: 822–827.

Åström S, Stenlund H & Lindén C (2007): Incidence and prevalence of pseudo-exfoliation syndrome and open-angle glaucoma in northern Sweden. Part I & II. Acta Ophthalmol Scand **85**: 828–837.

Jeng SM, Karger RA, Hodge DO, Burke JP, Johnson DH & Good MS (2007): The risk of glaucoma in pseudoexfoliation syndrome. J Glaucoma **16**: 117–121.

Jonasson F, Damji KF, Arnarsson A, Sverrisson T, Wang L, Sasaki H & Sasaki K (2003): Prevalence of open-angle glaucoma in Iceland: Reykjavik Eye Study. Eye **17**: 747–753.

Lindberg JG (1989): Clinical investigations on pigmentation of the papillary boarder and translucency of the iris in cases of senile cataract and normal eyes in elderly persons. Acta Ophthalmol **67**(Suppl. 190): 1–96.

Ringvold A (1999): Epidemiology of the pseudo-exfoliation syndrome. Acta Ophthalmol Scand **77**: 371–375.

Schlotzer-Schrehardt U & Naumann GO (2006): Ocular and systemic pseudoexfoliation syndrome. Am J Ophthalmol **141**: 921–937.

Tarkkanen A, Reunanen A & Kivelä T (2007): Frequency of systemic vascular diseases in patients with primary open-angle glaucoma and exfoliation glaucoma. Acta Ophthalmol Scand (in press).

Thorleifsson G, Magnusson KP, Sulem P et al. (2007): Common sequence variants in the *LOXL1* gene confer susceptibility to exfoliation glaucoma. Science **317**: 1397–1400.