Exfoliation glaucoma: clinical perspective of a global challenge

Glaucoma pseudo-exfoliativo: perspectivas clínicas de um desafio global

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INTRODUCTION

Exfoliation syndrome (XFS) may be defined as a discrete clinical entity characterised by the synthesis and deposition of fine white granular material, upon and within ocular and orbital tissues [1, 2]. It is now considered the most common identifiable specific entity leading to the development of glaucoma [3]. Recent evidence suggests that XFS may be a systemic condition [4] although, as yet, there is no conclusive evidence that XFS may cause damage systemically. The diagnosis of XFS is based on the incidental finding of "dandruff-like" material upon the pupillary margin, or "sugar frosting" of the anterior lens capsule [5]. XFS is one of the most controversial subjects in the ophthalmic literature [6, 7]. Numerous reports have discussed the controversy over the morphology, origin and pathogenesis of the condition [1, 5, 8, 9]. From the clinical standpoint, controversy has arisen concerning both the epidemiological and the clinical features of XFS [5, 10-13]. Even the nomenclature of XFS remain debatable: exfoliation, exfoliative, pseudoexfoliation syndrome are current terms used to describe the condition. A detailed account of the history, morphology, controversy and literature of XFS is beyond the scope of this short review. The reader is referred to detailed reviews of the early literature by Sunde [14], Tarkkanen [11], Layden & Shaffer [7] and more recently by Ritch [4]. The following description merely outlines a number of important clinical features of exfoliation glaucoma (XFG), a clinical challenge which is an important cause of visual loss worldwide.

Exfoliation glaucoma: a global challenge

Exfoliation glaucoma (XFG) is a secondary glaucoma arising in a significant number of eyes with XFS. It is both common and an important cause of visual loss, especially in some glaucoma cohorts [13, 15, 16]. The important current and future role of XFG in causing visual disability in the elderly has been recently highlighted by some authors [3-5, 12, 17, 18]. In Sweden, Thorburn [19] calculated that 2.5% of the population over the age of 70 years developed field loss due to XFG. Raivio [20] has estimated that the number of patients with glaucoma, especially XFG, in Finland will increase by 40% by the year 2010. Consequently, he calculated that a 40% increase of resources and glaucoma care facilities will be required for glaucoma patients by the year 2010. Demographic trends in Europe suggest that the number of XFG patients will steadily increase in the future due to increasing life expectancy in countries where the disease is most prevalent.

Unfortunately, general terms such as "primary open angle glaucoma" and "chronic open angle glaucoma" are often used to include both XFG and POAG and numerous studies fail even to consider XFG. This approach is inappropriate since XFG and POAG are different entities. Clinical and morphological evidence supports the view that XFG is a true secondary open-angle glaucoma. The balance of ultrastructural evidence is in favour of XFG developing due to an accumulation of exfoliation material and pigment, or both, within the outflow system of the affected eye [1, 9]. Clinically, XFG has a number of specific attributes which distinguish it from POAG [4, 5, 12].

Prevalence

The early literature, based on ophthalmic cohorts, advanced the notion that the XFS is common in Scandinavia and Greece, but rare in other countries e.g. Germany, Britain and the United States [15]. However, in the literature of the late sixties and seventies the concept of XFS being an uncommon disease in most ethnic groups was challenged. Aasved [21] provided convincing epidemiological evidence to suggest that the prevalence of XFS in population groups is first, much higher than previously thought and second, similar in all geographic areas. Subsequent studies, mostly in ophthalmic cohorts, have either supported, or contradicted Aasved's view.

In any assessment of the true prevalence of XFS it must be remembered that figures based on ophthalmic patients show a

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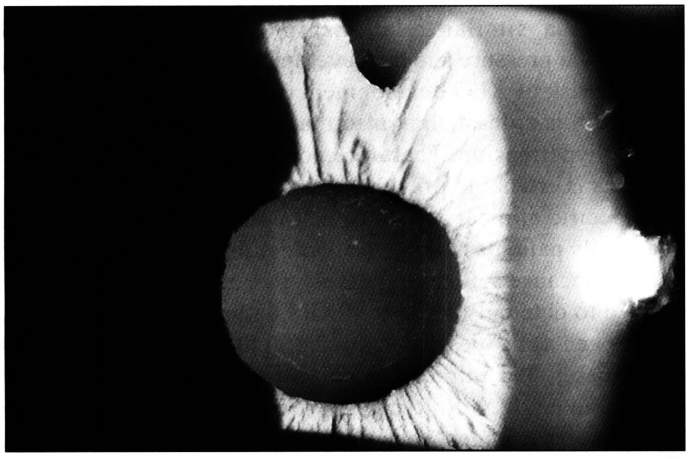

Fig. 1 - Appearance of central disc in an operated patient with XFG.

biased prevalence for this disorder [13, 22]. On the other hand, XFS is a chronic disorder with a slow and insidious onset and subtle signs which are difficult to see clinically [10, 12].

Epidemiological data collected by the same investigator from different ethnic cohorts may prove helpful. We conducted a recent epidemiological study in a Greek surgical cohort [23] and compared these data with that obtained in a prospective study with a similar protocol in Scotland [24]. In the Scottish surgical cohort the prevalence of XFG was 26%, a prevalence which was significantly lower than that in the Greek study 74%. The latter prevalence is similar to the figures reported in Scandinavian cohorts (50-62%). Therefore, XFG appears to be subject to significant geographic variation. Nevertheless, there is often a tendency for underdiagnosis and this problem may be partly due to the subtlety of the

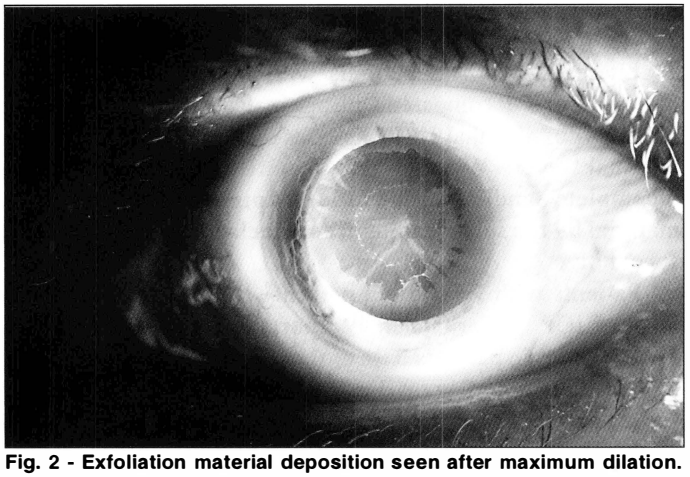

Fig. 2 - Exfoliation material deposition seen after maximum dilation.

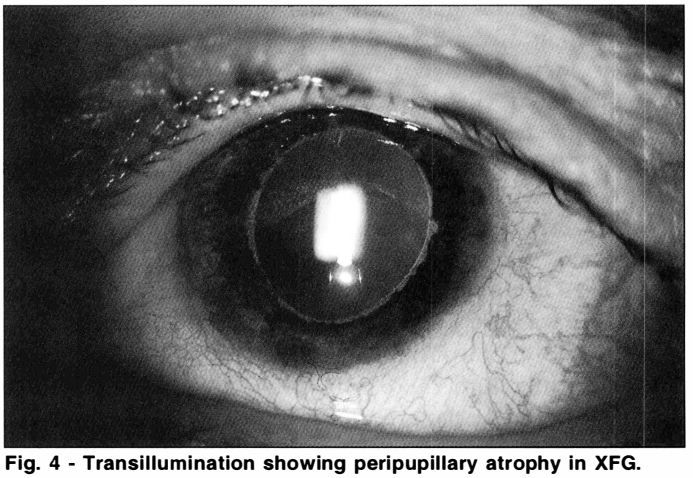

Fig. 4 - Transillumination showing peripupillary atrophy in XFG.

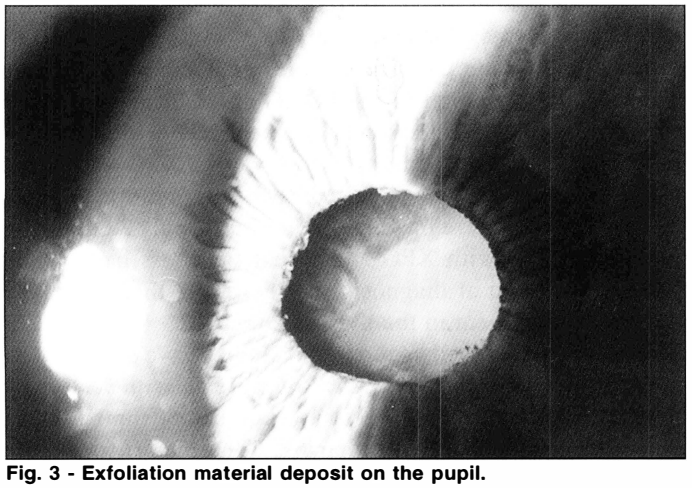

Fig. 3 - Exfoliation material deposit on the pupil.

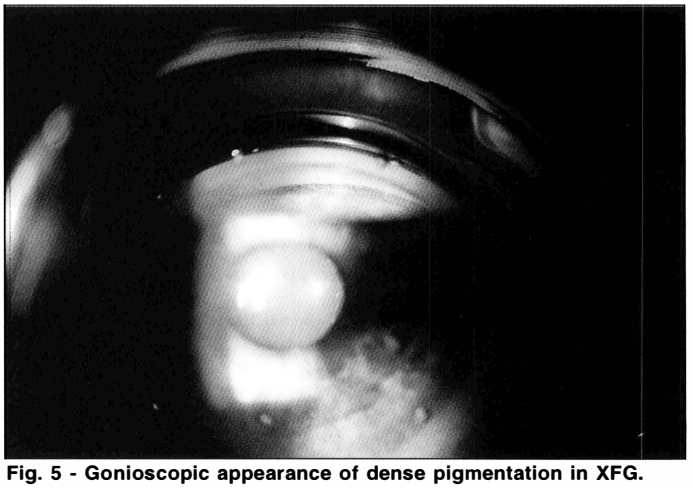

Fig. 5 - Gonioscopic appearance of dense pigmentation in XFG.

diagnostic signs and the poorly defined early stages of XFS. Thus, the true prevalence of the condition remains uncertain in many countries [4, 13].

In the present state of knowledge it is possible to say that XFS is age-dependent, its prevalence increases uniformly with age and a significant proportion of the elderly population is affected. In certain countries such as Greece, Finland, Norway and Iceland available data suggest that 12-30% of the population over the age of 70 years show evidence of exfoliation material on clinical examination [13].

The percentage of patients with XFS who have XFG, or ocular hypertension on initial examination ranges from 22 to 94% depending on the sampling method [2, 15, 25, 26]. A retrospective American study [27] has shown that in patients with XFS and normal intraocular pressure (IOP), 5% developed raised IOP over 5 years, while 15% did so over 10 years. Some authors felt that XFG occurred shortly after the development of XFS, otherwise the risk was small [28], however, the general consensus is that XFG may ensue at any time in a patient with XFS and unilateral involvement constitutes an earlier stage in the evolution of the disorder [6, 29]. Whether XFG can occur without an interval of normality, i.e. without the initial development of XFS, is not known. There is a significant risk to the unaffected eye with XFS developing XFG, related to the duration of the condition [30, 31]. A retrospective study [29] has indicated that 21-26% of patients with bilateral XFS and unilateral XFG may develop XFG in the fellow eye within 5 years. In a series of 519 patients, Brooks & Gillies [32] established that in unilateral XFG the presence of XFS in the fellow eye was a serious risk factor. Raised IOP developed in approximately 75% of these eyes.

In the literature there is conflicting evidence on the influence of sex on the prevalence and severity of EXG. The impressions of previous workers [12, 31] that XFG may affect more severely males have not been entirely confirmed by a recent study comparing XFG and POAG [23]. Although more males with XFG required surgery in this study, the same trend was evident amongst POAG patients. This implies that other factors like compliance to antiglaucoma therapy contribute to the higher prevalence of male patients in surgical cohorts. This is also supported by the absence of sex-related difference in the level of IOP prior to surgery.

The heredity pattern for XFG remains unknown but the majority of cases are sporadic. Tarkkanen [28] detected 26 patients with family history of glaucoma among 418 patients with the condition.

Exfoliation glaucoma vs primary open-angle glaucoma

The occurrence of XFG in a significant proportion of patients with XFS is firmly established but at the present time it is impossible to say which mechanism is responsible for the development of XFG in patients with XFS or what factors protect XFS patients from XFG. A significant number of patients with XFS do not develop XFG in their lifetime. However a similar relationship exists between raised intraocular pressure and the development of POAG. It appears that the risk of XFG development (1.5% per year) in patients with XFS is at least similar to that of POAG in patients with ocular hypertension. Therefore, long term monitoring of XFS patients is crucial in preventing visual loss from XFG.

Specific clinical attributes distinguish XFG from POAG. Generally patients with XFG are older than those with POAG; this is because XFS is relatively rare under the age of 50. Indeed to date only 5 cases of XFS under the age of 40 years have been fully described in the ophthalmic literature: all these cases had intraocular surgery performed prior to the development of XFS. Recently we reported XFS in a 17 year old girl, the youngest case reported to date [33]. Asymmetry in the clinical manifestation of XFG is the rule rather than the exception [10]. In contrast to POAG, patients with XFG present more often with unilateral glaucoma. Indeed there are patients with bilateral XFS and severe unilateral XFG who never develop raised IOP in the contralateral eye. Lindblom & Thorburn [34, 35] found bilateral glaucoma at presentation in only 31% of XFG patients compared with 54% for POAG patients.

Interestingly, XFS patients without glaucoma exhibit a higher mean IOP compared with age matched control subjects [36]. It is thus possible that XFS increases outflow resistance even in "normal" eyes. Whether this feature is explained by the incomplete handling of the influx of pigment and exfoliation material by the self-cleaning filter mechanism of the angle, is speculative.

Patients with XFG often present with a particularly high level of IOP [37]. Tarkannen [11] reported that over 60% of the affected eyes in patients with unilateral XFG exhibited an IOP higher than 35 mmHg, at diagnosis. Lindblom & Thorburn [34] surveyed the hospital records of a well defined glaucoma population in Halsingland, Sweden. Their cohort consisted of 245 cases with XFG and 75 cases with POAG. Both glaucomas showed the same degree of visual field loss at diagnosis, despite the fact that the mean IOP at diagnosis was considerably higher in the XFG group (42.9 mmHg for XFG versus 34.8 mmHg for POAG). In XFG these authors noted a significant increase in the mean IOP with every stage of progression in their classification for glaucomatous damage. This was not observed in the POAG cases. It is remarkable that, according to their findings, the mean IOP at diagnosis for patients with legal blindness due to advanced XFG was almost 60 mmHg. This is also supported by the observation that low IOP is extremely rare in XFG. In one study, only 2 out of 245 patients (0.8%) with XFG and visual field loss had an IOP below 20 mmHg at diagnosis [35]. Therefore, there is nearly universal agreement in the literature that XFG is a hypertensive glaucoma. Indeed, a number of studies have described an acute form of XFG. Up to 25% of patients with XFG may present with an acute rise in IOP in excess of 50 mmHg, and a varied degree of corneal oedema [37]. The majority of these cases have open angles, although cases of acute angle closure

glaucoma with exfoliation have also been described [4]. Extreme cases of so called "absolute XFG" can occasionally present with high IOP and no perception of light. In an Australian series, 5 cases of absolute XFG were identified in a cohort of 72 cases with acute open angle XFG [37]. There are data indicating a higher prevalence of narrow/closed angle in association with exfoliation [4]. Furthermore, documentation of the degree of angle pigmentation is considered a reliable indicator of the severity of XFG. In one study, 81% of the more heavily pigmented eyes showed the more severe XFG [38]. In contrast, exfoliation material deposition within the angle in not a reliable indicator of the risk of development, or the severity of XFG. A characteristic gonioscopic feature termed Sampaolesi's line, defined as a single wavy pigmented line superior to Schwalbe's line, has also been documented in nearly all cases with XFG and is a reliable diagnostic indicator [12, 39].

Characteristically, patients with XFG may suffer a transient acute IOP elevation after mydriasis. Gifford [10] described the appearance of a "pigment cloud" in the anterior chamber following mydriasis in 6 out of 62 cases. Among the differences between XFG and POAG one of the most interesting is the lack of a change in IOP following the use of topical steroids. Steroid-induced ocular hypertension occurs in approximately a third of the normal population, but occurs in the majority of patients with POAG. It is reversible, reproducible and genetically determined, the trabecular meshwork is the site of pathology responsible for the IOP elevation and the response is abolished following filtering surgery [26]. XFG differs markedly from POAG by exhibiting the same frequency of steroid response as that of the normal population [12, 40].

XFG has uniformly been considered as a severe form of chronic open angle glaucoma [5, 41-43]. The reasons for this, however, have not been adequately documented. In a retrospective study, Olivius & Thorburn [44] reported that after 5 years more glaucomatous damage had occurred in the XFG patients that in those with POAG in spite of recourse to surgery more often and earlier. After 5 years the XFG group exhibited severe visual fields loss in 48% of cases compared with only 19% in the POAG group. Pohjanpelto [30] studied retrospectively the fate of visual fields in 42 eyes with XFG and 46 eyes with POAG. At the end of the follow up period (mean 10 years), 71% of the eyes in the XFG group and 82% of the eyes in the POAG group had deteriorated. Almost 40% of the eyes with XFG and 26% of the eyes with POAG had become legally blind. In a retrospective study in Sweden, it was established that 2.5% of all individuals over the age of 70 years, developed visual field defects due to XFG within their lifetime [19]. In the same study, it was established that almost 0.8% of individuals aged 70 or more lost vision in one eye and 0.3% were visually handicapped by bilateral XFG before death.

In a recent prospective study we evaluated the diurnal IOP in XFG compared to POAG [45, 46] to determine its potential role in the course and management of this disease. Patients with XFG showed significantly higher mean diurnal range of IOP (13.5 mmHg versus 8.5 mmHg for POAG), higher maximum IOP (mean 38.2 mmHg versus 26.9 mmHg for POAG) and higher minimum IOP (mean 24.7 mmHg versus 18.4 mmHg for POAG). When compared to POAG, patients with XFG demonstrated more often an IOP range higher than 15 mmHg (35% vs only 7.5% for POAG). Importantly, in 45% of XFG patients and in 22.5% of POAG patients the peak levelle pigmentation is considered a reliable pathognomic feature of XFG. Furthermore, gonioscopic documentation of the degree of angle pigmentation of a glaucomatous eye is considered a rn XFG the worse IOP characteristics may account for the more rapid glaucomatous degeneration compared to POAG. Weber et al. [47] have suggested that in patients with secondary glaucomas, as opposed to POAG, good correlation between visual field decay and both mean IOP and maximum IOP existed. Stewart et al. [48] have demonstrated the importance of low variance in IOP over time in preserving visual function in advanced glaucoma.

Once medical treatment of XFG is started several authors have noted that, in comparison with POAG, the response to medical therapy is poorer [5, 28, 31]. Another feature stressed by some writers is that an initial good response to medical therapy is followed upon by a rising IOP and sometimes abrupt failure in IOP control [49]. Airaksinen [50] compared the hypotensive effect of timolol to that of pilocarpine in patients with POAG and XFG. He concluded that in XFG a good hypotensive effect with timolol was followed by a rise in IOP later, so adjunctive medical therapy had to be added more frequently in XFG. Aasved et al. [49] found that the percentage of initial successful control (defined as IOP < 22 mmHg) with timolol in patients with XFG was only 11%. Blika & Saunte [51] reported that after 3 years on timolol drops alone successful control was obtained in 33% of the POAG cases compare in 6 out of 8 patients wi. Granstrom [42] documented retrospectively a greater risk of visual field loss in patients with XFG, compared with POAG patients, treated with pilocarpine 4% three times a day. Overall monotherapy is less successful in XFG compared to POAG.

We documented the diurnal IOP variation in XFG and POAG subjects treated with timolol maleate solution 0.5% b.i.d. [46]. Despite a greater percent reduction in IOP in XFG than POAG the absolute levels of IOP still remained higher in XFG after timolol treatment. Only 13% of XFG patients vs. 32% of POAG patients achieved a level of IOP consistently 18 mmHg or below throughout the 24 hour period. Considering a higher target for treated IOP we found that 37% XFG versus 58% of POAG patients maintained treated IOP values 21 mmHg or below. The time of maximum IOP elevation in XFG patients receiving timolol generally was observed at 22:00 and 6:00 hours and importantly, 57% of EXG and 53% of POAG patients had their peak IOP outside office hours. Consequently, relying on a single office measurement to assess treatment response in XFG may not accurately reflect

the diurnal range of IOP. These IOP findings following timolol treatment may provide a reason why treated XFG patients progress more quickly and eventually suffer more often from severe visual loss.

The high IOP levels probably account for the higher risk of developing central retinal vein occlusion with XFG[26]. Gillies[41] reported 17 cases with central vein occlusion in a retrospective series of 250 patients with the condition. Tarkkanen[28] stressed the risk of neovascular glaucoma in XFG quoting a histological series of Finnish patients where approximately 33% of all eyes enucleated for neovascular glaucoma caused by central vein occlusion had co-existent XFS.

Argon Laser Trabeculoplasty (ALT) has certain characteristic attributes in XFG mainly due to the excess pigmentation in the angle which often obscures the location of the trabecular meshwork. An acute elevation of IOP in the immediate postoperative period was shown to be more common in XFG. Several studies have suggested that ALT is more successful in XFG, but this view is not universally shared [12]. Most authors have claimed a better initial response to ALT in XFG, due to the increased pigmentation of the trabecular meshwork. Tuulonen et al. [52] reported four factors which favour the use of ALT; older age, lower pre-treatment IOP level, XFG and pigmented meshwork. Advancing age and XFG are factors consistently reported to influence positively the outcome of ALT [4]. Svedbergh [53] reported a 70% initial success rate in 55 eyes with XFG and late failure only in 2 cases. Psilas and coworkers [54] obtained an average initial reduction of 46% (13.4 mmHg) in XFG compared to a reduction of 22% (9.2 mmHg) in POAG. Nevertheless, despite the higher initial IOP reduction there was no difference in the success rate of ALT between the two glaucomas approximately 2 years after treatment.

Higginbotham & Richardson [55] reported that despite having a large immediate IOP response to ALT exfoliation patients failed at a faster rate. A high rate of failure in XFG, compared to POAG, has been reported with longer follow up periods. In his review article in 1988 Svedbergh revised his view on the outcome of ALT in XFG on account of the increased rate of late failures. His 5 year retrospective analysis of 74 patients treated by ALT showed similar failure rates at the end of the first year in both XFG and POAG (19%) but, after 5 years late failures were significantly more common in the XFG group (69% versus 45% for POAG).

There are few studies on the results of surgery in POAG and XFG. Jerndal & Lundstrom [56] documented a similar rate of complications with that seen in POAG and a favourable IOP lowering effect in XFG. Tornqvist and Drolsum [57] provided a retrospective comparison with POAG after trabeculectomy. They identified better field preservation following surgery in XFG patients in comparison with comparable POAG patients. A recent prospective study in Glasgow [24] identified a significantly lower postoperative IOP for XFG than in comparable POAG patients, at approximately 6 months after surgery. A characteristic preoperative feature in XFG [23], was that despite treatment with more antiglaucoma drops for a shorter duration of time, at the time of surgery the mean treated IOP was still significantly higher than that for comparable POAG patients. Furthermore, XFG patients were more often treated surgically due to unacceptably high IOP, whilst progressive loss of visual field without recognised high IOP was more frequent in POAG. It was evident from our study that in many cases surgery is delayed. Therefore, early surgical intervention should be the course of action in XFG when initial medical and laser responses are deemed inadequate.

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