Exfoliation glaucoma: clinical perspective of a global challenge

Glaucoma pseudo-exfoliativo: perspectivas clínicas de um desafio global

Anastasios G. P. Konstas

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. It is now considered the most common identifiable specific entity leading to the development of glaucoma. Recent evidence suggests that XFS may be a systemic condition 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. XFS is one of the most controversial subjects in the ophthalmic literature. Numerous reports have discussed the controversy over the morphology, origin and pathogenesis of the condition. From the clinical standpoint, controversy has arisen concerning both the epidemiological and the clinical features of XFS. 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, Tarkkanen, Layden & Shaffer and more recently by Ritch. 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. The important current and future role of XFG in causing visual disability in the elderly has been recently highlighted by some authors. In Sweden, Thorburn calculated that 2.5% of the population over the age of 70 years developed field loss due to XFG. Raivio 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. Clinically, XFG has a number of specific attributes which distinguish it from POAG.

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. 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 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...
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 \(^{21}\) 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
diagnostic signs and the poorly defined early stages of XFS. Thus, the true prevalence of the condition remains uncertain in many countries. 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.

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. A retrospective American study 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, 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. 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. A retrospective study 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 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 XFG. The impressions of previous workers that XFG may affect more severely males have not been entirely confirmed by a recent study comparing XFG and POAG. Although more males with XFG required surgery in this study, the same trend was evident among 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 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. Asymmetry in the clinical manifestation of XFG is the rule rather than the exception. 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 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. 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. Tarkkanen reported that over 60% of the affected eyes in patients with unilateral XFG exhibited an IOP higher than 35 mmHg, at diagnosis. Lindblom & Thorburn 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. 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. The majority of these cases have open angles, although cases of acute angle closure...
Exfoliation glaucoma: clinical perspective of a global challenge

glaucoma with exfoliation have also been described. 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. There are data indicating a higher prevalence of narrow/closed angle in association with exfoliation. 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. 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.

Characteristically, patients with XFG may suffer a transient acute IOP elevation after mydriasis. Gifford 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. XFG differs markedly from POAG by exhibiting the same frequency of steroid response as that of the normal population.

XFG has uniformly been considered as a severe form of chronic open angle glaucoma. The reasons for this, however, have not been adequately documented. In a retrospective study, Olivius & Thorburn 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 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. 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 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 IOP is considered a reliable pathognomonic feature of XFG. Furthermore, gonioscopic documentation of the degree of angle pigmentation of a glaucomatous eye is considered a characteristic XFG that the worse IOP characteristics may account for the more rapid glaucomatous degeneration compared to POAG. Weber et al. 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. 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. 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. Airaksinen compared the hypertensive effect of timolol to that of pilocarpine in patients with POAG and XFG. He concluded that in XFG a good hypertensive 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. found that the percentage of initial successful control (defined as IOP < 22 mmHg) with timolol in patients with XFG was only 11%. Blika & Saunte reported that after 3 years on timolol drops alone successful control was obtained in 33% of the POAG cases compared in 6 out of 8 patients with XFG. Granstrom 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. 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 53% 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 XFG 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 XFG26. Gillies41 reported 17 cases with central vein occlusion in a retrospective series of 250 patients with the condition. Tarkkanen28 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 13. 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 58 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 33, 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.

REFERENCES

1. Morrison JC & Green WR. Light microscopy of the exfoliation syndrome. Acta Ophthalmol 1988;184(Suppl):5-27.
2. Dimitrakoulia N, Konstas AG, Ringvold A, Stefanionou M, Tarkkanen A. Exfoliation glaucoma. Ophthalmologica 1995;7:329-39.
3. Ritch R. Exfoliation syndrome: the most common identifiable cause of open-angle glaucoma. J Glaucoma 1994;3:176-8.
4. Ritch R. Exfoliation syndrome. In: The Glaucomas, eds. Ritch R, Shields MB, Krupin T, 2nd Ed. Mosby, St. Louis 1996,993-1022.
5. Konstas AGP, Dimitrakoulia N, Konstas PA. Exfoliation syndrome and open angle glaucoma. Klin Monatsbl Augenheilkd 1993a;202:259-68.
6. Bertelsen TI. Fibrillopathia epithelioarcapsularis. The so-called senile exfoliation or pseudoexfoliation of the anterior lens capsule. Acta Ophthalmol 1966;44:737-50.
7. Layden WE & Shaffer RN. Exfoliation syndrome. Trans Am Ophthalmol Soc 1973;71:128-51.
8. Dickson DH & Ramsey MS. Fibrillopathia epithelioarcapsularis. Review of the nature and origin of pseudoexfoliative deposits. Trans Ophthalmol Soc U K 1979;99:284-92.
9. Dark AJ & Streeters BAW. Pseudoexfoliation syndrome. In: Garner A & Klintworth G (eds). Pathobiology of ocular disease. A dynamic approach, Marcel Dekker, New York, 1982;1303-20.
10. Gifford H. A clinical and pathologic study of exfoliation of the lens capsule. Am J Ophthalmol 1958;46:508-24.
11. Tarkkanen A. Treatment of chronic open-angle glaucoma associated with pseudoexfoliation. Acta Ophthalmol 1965;43:514-23.
12. Jerndal T. Open angle glaucoma and the pseudoexfoliation syndrome. In: Cairns JE (ed). Glaucoma. Grune & Stratton, London. 1986;661-77.
13. Forsius H. Exfoliation syndrome in various ethnic populations. Acta Ophthalmol 1998;184(Suppl):71-85.
14. Sunde AO. On the so called exfoliation or pseudoexfoliation of the anterior lens capsule. A clinical and anatomical study. Acta Ophthalmol Suppl 1956;45:7-85.
15. Aasved H. The geographic distribution of fibrillopathia epithelioarcapsularis, so-called senile exfoliation, or pseudoexfoliation of the anterior lens capsule. Acta Ophthalmol 1969;792-810.
16. Ringvold A, Blika S, Elas T et al. The Middle-Norway eye screening study. I. Epidemiology of pseudo-exfoliation syndrome. Acta Ophthalmol 1988;66:652-8.
17. Konstas AG & Allan D. Pseudoexfoliation glaucoma in Greece. Eye 1989;3:747-53.
18. Stefanionou M, Petroutes G, Psilas K. The frequency of pseudoexfoliation in a region of Greece (Epirus). Acta Ophthalmol 1990;68:307-9.
19. Thorburn W. The outcome of visual function in capsular glaucoma. Acta Ophthalmol 1988;184(Suppl):132-7.
20. Raivoi I. Number of glaucoma patients in Finland in the year 2010. Acta Ophthalmol 1987;182(Suppl):21-23.
21. Aasved T. The frequency of fibrillopathia epithelioarcapsularis (so called senile exfoliation or pseudoexfoliation) in patients with open-angle glaucoma. Acta Ophthalmol 1971a;49:194-209.
22. Konstas AGP, Dimitrakoulia N, Kourtizidou O et al. Frequency of exfoliation syndrome in Greek cataract patients. Acta Ophthalmol Scand 1996;74:478-82.
23. Konstas AGP, Tatsios I, Kardassopoulou A, Bufidis T, Maskaleris G. Preoperative features of patients with exfoliation glaucoma and primary open-angle glaucoma. The AHEPA study. Acta Ophthalmol 1997,(in press).
Exfoliation glaucoma: clinical perspective of a global challenge

24. Konstas AGP, Jay JL, Marshall GE, Lee WR. Prevalence, diagnostic features and response to trabeculectomy in exfoliation glaucoma. Ophthalmology 1993b;100:619-27.
25. Kozart DM & Yanoff M. Intraocular pressure status in 100 consecutive patients with exfoliation syndrome. Ophthalmology 1982;89:214-8.
26. Konstas AGP. Morphological and clinical studies on the exfoliation syndrome and open angle glaucoma. Glasgow. PhD Thesis 1993;1-364.
27. Henry JC, Krupin T, Schmitt M et al. Long-term follow-up of pseudoexfoliation and the development of elevated intraocular pressure. Ophthalmology 1987;94:545-52.
28. Tarkkanen AH. Pseudoexfoliation of the lens capsule. Acta Ophthalmol 1983.70:9-18.
29. Hansen E & Sellevold OJ. Pseudoexfoliation of the lens capsule. II. Development of the exfoliation syndrome. Acta Ophthalmol 1969;47:161-73.
30. Pohjanpelto P. Long term prognosis of visual field in glaucoma simplex and glaucoma capsulare. Acta Ophthalmol 1985;63:418-23.
31. Montanes JM, Serna AA, Paredes AA. Pseudoexfoliative glaucoma in patients with open-angle glaucoma in the northwest of Spain. Acta Ophthalmol 1990;68:695-9.
32. Brooks AMV & Gillies WE. The presentation and prognosis of glaucoma in pseudoexfoliation of the lens capsule. Ophthalmology 1988;95:271-76.
33. Konstas AGP, Ritch R, Bufidis T et al. Exfoliation syndrome in a 17-year-old girl. Arch Ophthalmol 1997a;115:1063-7.
34. Lindblom B & Thorburn W. Observed incidence of glaucoma in Halsingland, Sweden. Acta Ophthalmol 1984a;62:217-22.
35. Lindblom B & Thorburn W. Functional damage at diagnosis of primary open angle glaucoma. Acta Ophthalmol 1984;62:223-9.
36. Aasved H. Intraocular pressure in eyes with and without fibrillopathy epithelioepithelialis. Acta Ophthalmol 1971b;49:601-10.
37. Gillies WE & Brooks AMV. The presentation of acute glaucoma in pseudoexfoliation of the lens capsule. Aust N Z J Ophthalmol 1988;16:101-6.
38. Wishart PK, Speth GL & Poryzees EM. Anterior chamber angle in the exfoliation syndrome. Br J Ophthalmol 1985;69:103-7.
39. Sampaolo R, Zarate J, Croxato O. The chamber angle in exfoliation syndrome. Acta Ophthalmol 1988;184(Suppl):48-53.
40. Gillies WE. Corticosteroid-induced ocular hypertension in pseudo-exfoliation of the lens capsule. Trans Ophthalm Soc U K 1978;98:96-100.
41. Gillies WE. Secondary glaucoma associated with pseudoexfoliation of the lens capsule. Trans Ophthalmol Soc U K 1970;70:90-5.
42. Granstrom PA. Progression of visual field defects in glaucoma. Relation to compliance with pilocarpine therapy. Arch Ophthalmol 1985;103:529-31.
43. Konstas AGP, Stewart WC, Stroman GA, Sine CS. Clinical presentation and initial treatment patterns in patients with exfoliation glaucoma versus primary open-angle glaucoma. Ophthalmic Surg Lasers 1997a;28:111-7.
44. Olivius E & Thorburn W. Prognosis of glaucoma simplex and glaucoma capsulare. A comparative study. Acta Ophthalmol 1978;56:921-34.
45. Konstas AGP, Mantziris DA, Stewart WC. Diurnal intraocular pressure in untreated exfoliation and primary open-angle glaucoma. Arch Ophthalmol 1997b;115:182-5.
46. Konstas AGP, Mantziris DA, Cate EA, Stewart WC. Effect of timolol on the diurnal intraocular pressure in exfoliation and primary open-angle glaucoma. Arch Ophthalmol 1997c;115:975-9.
47. Weber J, Koll W, Kriegelstein G. Intraocular pressure and visual decay in chronic glaucoma. German J Ophthalmol 1993;2:165-9.
48. Stewart WC, Chorak RP, Hunt HH, Sethuraman G. Factors associated with visual loss in patients with advanced glaucomatous changes in the optic nerve head. Am J Ophthalmol 1993;116:176-81.
49. Aasved H, Seland JH, Slaegsvoed JE. Timolol maleate in treatment of open angle glaucoma. Acta Ophthalmol 1979;57:700-8.
50. Airaksinen PJ. The long-term hypotensive effect of timolol maleate compared with the effect of pilocarpine in simple and capsular glaucoma. Acta Ophthalmol 1979;57:425-34.
51. Blika S & Saun[...](continued)