

Factors in the exfoliation syndrome*

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SUMMARY The study cohort consists of 459 subjects over 60 years of age. Intraocular pressure and degrees of exfoliation, lens changes, and pigment were recorded and their interrelationships investigated. A raised intraocular pressure was found to be associated with exfoliation, as also was increased pigmentation and the development of lens changes. An original observation is that the exfoliated males had a significantly higher IOP than their female counterparts.

So-called 'pseudo exfoliation of the lens capsule' continues to arouse great interest because of the uncertainty surrounding the origin of the exfoliated material and its relationship to raised intraocular pressure. The continuing production of the exfoliated material in the absence of the lens¹⁻³ and the presence of the material outside the eye^{4,5} when it could not have got there via the uveoscleral canals⁶ confirms a more widespread distribution. Eagle *et al.*⁷ found it in the wall of a short posterior ciliary artery in the orbit, and they added further evidence that the material is a form of abnormal basement membrane. This would also explain the reason why the lens epithelium,^{8,9} the ciliary epithelium,² and the zonule¹⁰ have also been found to produce it. The name of 'the exfoliation syndrome'¹¹ is therefore more appropriate.

The liberation of pigment into the anterior chamber, with its deposition presumably by gravity in the lower part of the angle, coupled with the depigmentation of the iris and its abnormal vasculature,¹² is also part of the process.

Incidence rates for the syndrome reported to date are predominantly based on males and females combined and ignore possible sex variations. These reports have not been consistent,¹³⁻¹⁸ and it is suggested that a large-scale controlled study is required to clarify the issue. It is unusual under the age of 60.

While the existence of its relationship to glaucoma has been known for many years, the mechanism that produces the increase in intraocular pressure has never been clarified, and Pohjola and

Horsmanheim¹⁹ found that the steroid responders in cases with the exfoliation syndrome were no higher than those of the normal population. They postulated that two types of glaucoma processes are involved. The first is a primary simple glaucoma in which both eyes are involved and is steroid responsive. The second type, which is not steroid responsive, is secondary to the exfoliation and affects only one eye.

The frequency of cases of the syndrome in our glaucoma clinics (63%) prompted this investigation. The study was undertaken to elicit its prevalence, relationship with sex, age, intraocular pressure, lens changes, and the type and extent of pigment in the angle.

CLINICAL FEATURES

The syndrome is undetectable except with a slit-lamp or strong loupe. With an undilated pupil dandruff-like deposits are seen at the edge of the iris. When the pupil is dilated the appearance is of a granular peripheral zone and central disc on the superficial layers of the capsule, which present with the classical hoar frost appearance. Between these 2 is a normal-appearing ring of lens capsule which appears to be the area in contact with the moving iris, which supposedly keeps it clear of the deposits.¹⁴ The less usual appearance is that of a peeling of the thin superficial lamella of the capsule in which it becomes rolled, rather like an onion skin. Clumps of exfoliated material are seen in advanced cases on the posterior corneal surface and in the angle. The clumps are also seen on the vitreous face and the pupil edge after cataract extraction.

Increased quantities of pigment cells in the anterior chamber are a constant finding. They derive from the pigment epithelium on the back of the iris, circulate with the aqueous currents, and are washed into the

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Table 1 Indices constructed to measure exfoliation, lens changes, fixed and loose pigment

Exfoliation Grade		Lens Changes Grade	
0	None	0	None
I	Exfoliation confined to the periphery of the lens and not seen unless the pupil is dilated	I	Slight changes such as vacuoles, spots striae or early nuclear sclerosis
II	Flakes of exfoliated material on the edge of the iris or on the surface of the lens capsule or both	II	Marked clefts or nuclear sclerosis which make only a blurred view of the fundus possible
III	Flakes of exfoliated material in the angle or on the posterior corneal surface	III	Advanced lens changes so marked that no view of the fundus is possible
Fixed Pigment Grade		Loose Pigment Grade	
0	None	0	None
I	Slight browning of the trabecular network	I	Scattering of pigment on Schwalbes line below
II	Definite brown pigmentation of the network	II	Heavier deposits of pigment on Schwalbes line, in the Trabeculum and slightly on the surface of the iris below
III	Heavy infiltration of the network with dark brown or black pigment	III	Heavy clumps of black pigment granules below

trabecular network around the circumference of the angle. On slit-lamp examination the cells can be seen on the corneal endothelium as a Krukenberg spindle and visible as brown particles circulating in the aqueous. The pigment cloud sometimes seen when the pupil is dilated indicates the ease with which these cells are shed. The cells are deposited to a greater degree by gravity in the inferior one-sixth of the angle. Here they can be seen on gonioscopy as heavy black pigment deposits of varying degree on Schwalbe's line and in front of it, in the trabeculum, and on the surface of the iris below; we call these loose pigment. In the rest of the angle the deposits that are found only in the trabeculum into which they are washed by the aqueous are called fixed pigment. Thus while fixed and loose pigment are not exclusive, they represent the circulatory and gravitational deposition of pigment respectively.

HISTOLOGY

Davenger and Pedersen²⁰ described the histology of the pseudoexfoliated material as consisting of fibrils and a ground substance. The fibrils were of 2 types. Those noted on scanning electron microscopy were coiled in spirals, while those seen on transmission electron microscopy were straight or slightly bent. The main constituent seems to be mucopolysaccharides. The presence of these fibrils was confirmed by Dickson and Ramsay,²¹ who described 2 types of differing diameter. Both types were found on the lens, but only the ones of large diameter were found on the iris and ciliary body.

Materials and methods

The subjects examined in the study are in 3 groups, an exfoliated group, a clinic group, and control group aged over 60. The first group was obtained from the

outpatient department over a 6-year period because they had the syndrome. The second group was a random sample of clinic patients over 60 years of age. The third group was made up of subjects obtained from 3 geriatric homes, and thus enables the extent of the exfoliation syndrome in the over-60 population to be estimated.

The patients were examined by slit-lamp microscopy, gonioscopy, and applanation tonometry seated upright at the slit-lamp. When no evidence of exfoliated material was seen, the pupils were dilated with cyclopentolate 1% drops, because grade 1 is not visualised until this is done.

The following information was recorded for each subject: (a) sex; (b) age; (c) for each eye (1) pressure, (2) exfoliation, (3) lens changes, (4) fixed pigment, (5) loose pigment.

In quantifying or measuring exfoliation, lens changes, and fixed and loose pigment the observer is faced with the usual problems presented by qualitative information, and every effort was made in the construction of the indices to provide distinct and mutually exclusive categories. Reproducibility tests indicate that the following indices constructed for the present study are reliable (Table 1).

There were 459 study subjects, who were distributed by study groups and sex as listed in Table 2 (average age in brackets).

Table 2 Distribution of subjects by study group and sex

Study group	Sex		Total
	Male	Female	
Exfoliation	128 (69.8)	99 (72.9)	227 (71.2)
Clinic	33 (71.2)	71 (76.4)	100 (70.5)
Control	61 (70.7)	67 (70.1)	132 (75.6)
All	222	237	459

Table 3 *Distribution of cases by exfoliation*

<i>Exfoliation</i>	<i>Frequency</i>	<i>%</i>
None	189	43.6
Unilateral	63	14.5
Bilateral	181	41.9

There was no significant difference in age between the sexes in the study groups.

Results

The subjects were initially classified according to the presence/absence and extent of exfoliation (Table 3).

When we considered the exfoliated cases only, we found that 74% of these were bilaterally exfoliated. The average age of the bilateral cases was 72.1 years

the average pressure at each level of exfoliation, according to the classification used, for the unilateral and bilateral groups, there was no significant difference at grades I and II, but at grade III the average pressure for unilateral cases was significantly higher ($p < 0.05$).

The distribution of pigment of the 2 types measured is given in Table 4.

While degree of exfoliation was related to degree of pigmentation in both unilateral and bilateral groups, the pigmentation was generally more advanced in the bilateral cases. Finally, 64% of bilaterally exfoliated eyes had lens changes compared with 51% of the unilateral series (NS).

When the nonexfoliated eyes from the unilateral cases were compared to the eyes from normal cases, a small but significant increase in IOP was found, there

Table 4 *Percentage distribution of pigment for unilateral and bilateral exfoliated cases*

<i>Group</i>	<i>Fixed pigment</i>				<i>Loose pigment</i>			
	<i>Grade</i>				<i>Grade</i>			
	<i>0</i>	<i>I</i>	<i>II</i>	<i>III</i>	<i>0</i>	<i>I</i>	<i>II</i>	<i>III</i>
Unilateral	18%	42%	38%	2%	18%	38%	36%	8%
Bilateral	6%	44%	42%	8%	2%	35%	50%	14%

Table 5 *Comparison of nonexfoliated cases with nonexfoliated eyes from the unilateral series*

	<i>Fixed pigment</i>				<i>Loose pigment</i>				<i>Lens changes</i>				<i>IOP</i>
	<i>0</i>	<i>I</i>	<i>II</i>	<i>III</i>	<i>0</i>	<i>I</i>	<i>II</i>	<i>III</i>	<i>0</i>	<i>I</i>	<i>II</i>	<i>III</i>	<i>Mean (SEM)</i>
Eyes from nonexfoliated cases	72%	22%	5%	1%	39%	51%	9%	1%	52%	35%	10%	3%	16.7 (0.21)
Nonexfoliated eyes from unilateral series	36%	42%	16%	6%	22%	53%	22%	3%	57%	32%	7%	4%	18.5 (0.85)

compared with 70.1 years for the unilateral cases, but this difference was not statistically significant. There was no significant difference between the proportion of unilateral cases for males and females.

The average pressure of a unilaterally exfoliated eye was 31.4 mmHg compared with 30.5 mmHg for an eye from a bilaterally exfoliated case. Again this difference was not significant. When we considered

Table 6 *Average IOP level at each grade of exfoliation*

<i>Grade of exfoliation</i>	<i>Freq. (%)</i>	<i>IOP</i>	
		<i>Mean</i>	<i>SEM</i>
0	443 (50%)	17.0	0.22
I	90 (10%)	27.4	1.52
II	287 (32%)	31.6	0.89
III	72 (8%)	30.3	1.94

Table 7 *Frequency distribution of exfoliation by fixed and loose pigment (row percentages in parentheses)*

<i>Grade of exfoliation</i>	<i>Fixed pigment</i>				<i>Loose pigment</i>				
	<i>0</i>	<i>I</i>	<i>II</i>	<i>III</i>	<i>0</i>	<i>I</i>	<i>II</i>	<i>III</i>	
0	250 (68)	89 (24)	24 (7)	5 (1)	0	136 (37)	189 (51)	38 (10)	6 (2)
I	8 (21)	20 (51)	8 (21)	3 (8)	I	3 (8)	18 (46)	17 (44)	1 (3)
II	12 (7)	73 (39)	88 (47)	13 (7)	II	8 (4)	58 (31)	94 (51)	26 (14)
III	4 (8)	27 (52)	18 (35)	3 (6)	III	2 (4)	21 (40)	21 (40)	8 (15)

Table 8 Percentage distribution of pigment at each level of exfoliation

Grade of exfoliation	Fixed pigment				Loose pigment				
	0	I	II	III	0	I	II	III	
0	60 (73)	31 (20)	8 (6)	1 (1)	0	34 (38)	50 (52)	15 (8)	1 (2)
I	— (35)	63 (44)	25 (17)	12 (4)	I	— (13)	38 (52)	62 (31)	— (4)
II	4 (9)	43 (35)	46 (50)	7 (6)	II	1 (8)	36 (26)	52 (49)	12 (17)
III	— (12)	47 (55)	47 (27)	5 (6)	III	5 (3)	47 (36)	37 (42)	11 (18)

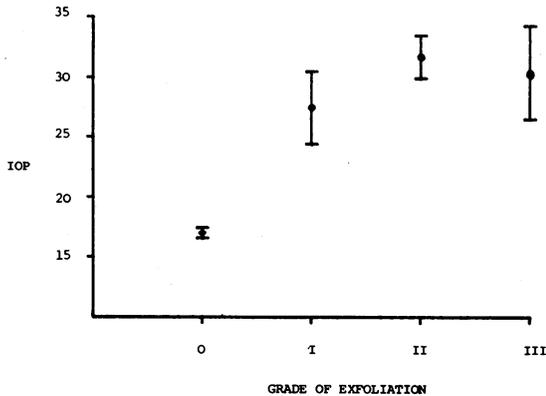


Fig. 1 Average IOP at each level of exfoliation (mean ± 2 SEM).

was greater fixed and loose pigment, while no difference in degree of lens changes was seen (Table 5).

RELATIONSHIPS OF EXFOLIATION

In order to evaluate in more detail the relationships of exfoliation, all eyes in the study were now pooled into 4 groups according to degree of exfoliation, and the average IOP for each level was calculated (Table 6).

The distribution of pigment, both loose and fixed, was next obtained (Table 7).

The association between pigment and exfoliation was highly significant ($p < 0.01$) in both cases. This is illustrated by the fact that only 32% of nonexfoliated eyes had fixed pigment of some degree compared with 92% of eyes with grade IV exfoliation. The corresponding figures for loose pigment were 63% and 96% respectively.

Further, the associated fixed pigment was more advanced at each grade of exfoliation for males, while the loose pigment was more advanced for males only at grade II exfoliation (Table 8).

The breakdown of exfoliation by lens changes is as follows (Table 9).

There was a strong relationship in this case also ($p < 0.01$), where 47% of nonexfoliated eyes had some lens changes compared with 72% for the exfoliated eyes.

Table 9 Frequency distribution of degree of lens changes for each grade of exfoliation (row percentages in parentheses)

Grade of exfoliation	Lens changes			
	0 I	II	III	IV
0	232 (53)	152 (35)	40 (9)	16 (4)
I	35 (37)	32 (36)	12 (13)	11 (12)
II	108 (38)	9 (32)	48 (17)	39 (14)
III	20 (28)	22 (31)	16 (23)	13 (18)
All	395 (45)	296 (33)	116 (13)	79 (9)

Since the main factors in the study have been shown to be related, it is important to investigate for possible interactions. An analysis of variance was carried out on IOP using degree of exfoliation, pigmentation, lens changes, and sex as explanatory variables. This analysis provided a very interesting and unexpected interaction between exfoliation and sex on IOP (Table 10).

This demonstrates clearly that the increase in IOP with exfoliation was significantly higher for males at every degree of exfoliation (I–III).

Since it is seen from Table 11 that the pressure response to exfoliation is severe generally only in the presence of fixed pigment, and that exfoliated females have less fixed pigment, it is necessary to investigate the effect of fixed pigment on the sex difference shown in Table 9.

However, even when controlled for the degree of fixed pigment, the average IOP was lower for females in most combinations of exfoliation and fixed pigment (Table 12).

The only other significant interaction was that

Table 10 Average IOP for each grade of exfoliation by sex

Grade of exfoliation	Intraocular pressure					
	Male			Female		
	Freq.	Mean	SEM	Freq.	Mean	SEM
0	189	17.1	0.36	253	16.8	0.28
I	49	30.8	2.27	40	23.3	1.77
II	162	34.2	1.17	125	28.1	1.31
III	31	35.8	3.21	41	26.2	2.25

Table 11 Average IOP at each grade of exfoliation and fixed pigment

Grade of exfoliation	Fixed pigment			
	0	I	II	III
0	16	17	20	22
I	17	28	34	—*
II	22	29	34	36
III	13	29	36	—

*Insufficient numbers of eyes to allow estimate.

Table 12 Average IOP at each grade of exfoliation and fixed pigment (female results in parentheses)

Grade of exfoliation	Fixed pigment				Number of eyes
	0	I	II	III	
0	16 (17)	18 (17)	19 (21)	23 (21)	149 (318)
I	— (17)	32 (24)	40 (28)	— (—)	16 (22)
II	25 (20)	32 (25)	37 (30)	43 (26)	101 (85)
III	— (13)	36 (25)	35 (36)	— (—)	19 (33)

Table 13 Average IOP at each grade of exfoliation and lens changes

Grade of exfoliation	Lens changes			
	0	I	II	III
0	17.2	16.4	16.8	18.4
I	30.4	24.5	30.7	22.5
II	32.4	34.0	29.2	25.5
III	34.9	26.9	29.5	27.1

between exfoliation and lens changes where the presence of severe lens changes seemed to reduce the hypertensive response to exfoliation (Table 13).

In the absence of exfoliation no significant difference in IOP was found with increasing lens changes. This was not the case in exfoliated eyes, where the average IOP for grade III lens changes was significantly lower ($p < 0.05$) than that for grade 0 lens changes at each level of exfoliation.

In the population group of 132 subjects there were 14 (11%) cases of exfoliation, 75% of whom had raised IOP (>22 mmHg) in the affected eye(s). Seven of these cases had unilateral exfoliation. The common occurrence of minor deposits of loose pigment in elderly people is confirmed in this group, where 65% were affected. Finally, 27% of the clinic group had some degree of exfoliation.

Discussion

The individual and combined effects of the different factors which make up the exfoliation syndrome have

been investigated. Their influence on the exfoliation/intraocular pressure relationship were also evaluated, and we found that the degree of pigmentation, extent of the lens changes, and sex were important elements.

We note that 50% of people aged over 60 have grade I loose pigment, and we think that this probably accounts for the conflicting reports on the influence of lower degrees of pigment deposition. Our study shows, however, that once grade II or III loose pigment occurs, the intraocular pressure rises to a pathological level. Previous observers have attributed the increase in intraocular pressure to blockage of the outflow channels by exfoliated material and pigment. Our studies show that the latter is the more important of the two.

A strong association between the development of lens changes and the exfoliative process has been found, but this may be a passive relationship as both are senile conditions. The more interesting finding is that advanced lens changes are associated with a small but significant decrease in the intraocular pressure in exfoliated eyes.

A sex association was of particular interest in that at each level of exfoliation a higher intraocular pressure was found in males. This unexpected result persists even when controlled for degree of fixed pigment (Table 12). Further research is obviously essential to substantiate the sex difference in the IOP response to exfoliation reported in this paper, and to explore the factors responsible for it.

The 74% of bilaterality is higher than average (50%–70%) but may be due to the age criterion in selection. We do, however, note a slight increase in the intraocular pressure in nonexfoliated eyes for the unilateral series, which agrees with Aasved's findings.¹⁵ We also noted that this is accompanied by a significant increase in the deposition of pigment. Thus investigation of nonexfoliated eyes in the unilateral series suggests a stochastic progression of fixed pigment deposition, an increase in the intraocular pressure, and the onset of exfoliation in that order.

To conclude, we emphasise the importance of pigmentation in the relationship between exfoliation and raised intraocular pressure. We point to the high incidence of exfoliation in patients over 60 years old who attend the hospital outpatient departments. We suggest that pigment is deposited initially and that this is followed by an increase in intraocular pressure and then the deposition of the exfoliated material.

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