

Prevalence of pseudoexfoliation syndrome among adults in Melmaruvathur

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Abstract

Aim: To determine the association of glaucoma in pseudo exfoliation syndrome, assess the status of blood aqueous barrier and to analyze the protein concentration in aqueous histo pathological changes in lens and trabecular meshwork in pseudo exfoliation syndrome. **Methodology:** A Prospective study of 100 patients with exfoliation syndrome who attended the OPD, department of Ophthalmology in Melmaruvathur Adiparasakthi institute of medical sciences between November 2015 and December 2017 were included in the study. All the patients were subjected to a detailed slit-lamp examination and Glaucoma workup was done for all the patients which included Gonioscopy with Goldmann Two mirror lens, Tonometry with Goldmaan applanation tonometer, Perimetry with Bjerrum's screen and Octopus 1-2-3 automated perimeter in selected cases. **Results:** Out of the 100 patients included, bilateral exfoliation was more common. Mean age of PXF was 64.5 years. 77% of patients had glaucoma of which open angle glaucoma accounted for 56 and angle closure glaucoma 21. Nuclear cataract had a more common incidence with exfoliation. Impairment of blood aqueous barrier is evidenced by rise mean aqueous protein and fluorescein dye leakage in angiography. On electron microscopic study shows duplication of basement membrane and intimate association of exfoliation material with basement membrane. **Conclusion:** Bilateral exfoliation was more common than unilateral. Exfoliation syndrome is definitely a risk factor for the development of glaucoma. The impairment of blood aqueous barrier is one of the pathognomonic features of exfoliation syndrome.

Key Words: Glaucoma – intra ocular pressure- gonioscopy-open angle - cataract- blood aqueous barrier.

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INTRODUCTION

Pseudo exfoliation is an age-related disorder in which abnormal fibrillogranular material of uncertain origin deposits mainly on the lens capsule, ciliary body, zonules, corneal endothelium and iris. It has been recently recognised as the most common identifiable cause of secondary open angle glaucoma in the world. Its poor response to medications makes it very difficult to treat. In

pseudo exfoliation the abnormal basement membrane in epithelial cells which is present thought the body produce fibrillar material. Apart from its deposition in anterior segment of eye it is also found in the walls of vortex vein and central retinal artery. There is also evidences of presence of fibrillar material in the extra ocular muscles, connective tissue in the orbit and in many vital organs. Its association with systemic disorders like TIA, Stroke, systemic hypertension and myocardial infarction is also documented by Robert Ritch in his study. The deposition of the fibrillar material in the anterior segment results in the alteration in the structures of the eye making cataract surgery challenging. The important pathologies in PXF are proteolytic disintegration of Zonules¹ with spontaneous fragmentation leading to zonular weakness and subluxation of lens and infiltration of iris stroma with extracellular matrix causing poor pupillary dilatation. Hence it's very important to meticulously examine the patient pre operatively to assess the Anterior chamber depth², pupil size after full mydriasis, zonular weakness,

phacodonesis, IOP etc to prevent complication during surgery. This Study was undertaken to analyse the association of glaucoma in pseudo exfoliation syndrome ,status of blood aqueous barrier and histo pathological changes in the lens and trabecular meshwork.

MATERIALS AND METHODS

A Prospective study of **100** patients with exfoliation syndrome³ who attended the OPD, department of Ophthalmology in *Melmaruvathuradiparasakthi institute of medical sciences* between November 2015 and December 2017 were included in the study. All patients provided informed and written consent. The selection criteria⁴ to study patients was the presence of exfoliation material on the lens or papillary margin. All the patients were subjected to a detailed slit-lamp examination and the following clinical signs were specifically were looked for Congestion, oedema, pigmentation, exfoliation material in cornea, Flare, Cells, depth, exfoliation material, pigment dispersion in anterior chamber. Pattern, Trans illumination defects in iris. Size, reaction to light, exfoliation material, dilatation with mydratics in pupil and exfoliation material, cataract present or not in lens. Pupil was dilated as a routine in all the cases to note the three zones of exfoliation material on the lens capsule. Glaucoma workup was done for all the patients which included Gonioscopy with Goldmann Two mirror lens, Tonometry with Goldmaan applanation tonometer, Permietry with Bjerrum’s screen and Octopus 1-2-3 automated perimeter in selected cases. During Gonioscopy⁵, besides assessing angle status, the presence of exfoliation material and increased pigmentation on the angle were also noted.

Blood Aqueous Barrier Assessment

- a. **Aqueous protein estimation:** Anteroir Chamber tapping for aqueous humour⁶ was done from 25 patients with exfoliation syndrome and 25 patients without exfoliation syndrome (for control) during cataract surgery using a tuberculin syringe through the clear cornea near the limbus. The tapped aqueous humour was subjected to biochemical estimation of total proteins by Biuret method. The protein levels in the two groups were compared. Care was taken while tapping to avoid contamination with blood since it might alter the protein level.
- b. **Iris Fluorescein angiography:** The blood aqueous barrier can also be assessed with iris fluorescein angiography, impairment of the barrier being evidence by increased dye leakage⁷. Iris fluorescein angiography was done at random in 10 patients with exfoliation syndrome and 10 non-exfoliation patients (for control).

ELECTRON MICROSCOPIC STUDY

Procedure: Specimens were taken from the lens and trabecular meshwork, of exfoliation patients obtained during cataract and anti-glaucoma surgery. They were straightaway fixed with 3% Buffered Glutaraldehyde, then post-fixed in 1% Osmium Tetraxodie and further dehydrated in ascending grades of alcohol and embedded in EPON – 812 (polar bed) resin. Ultra thin sections were taken in LKB5 ultra microtome and stained with Uranyl acetate and lead citrate. Electron micrographs were taken with Philips transmission electron microscope EM 420.

Statistical Analysis: The collected data was analysed with SPSS for windows, version 16.0, Chicago Inc. To describe about the data descriptive statistics frequency analysis, percentage analysis were used. To find the significant difference between the bivariate samples in Independent groups the Unpaired sample t-test was used. To find the significance in categorical data Chi-Square test was used. In the above statistical tool the probability value. 05 is considered as significant level. The study was reviewed by the appropriate ethics committee and was been performed in accordance with the ethical standards of the most recent version of the 1964 Declaration of Helsinki.

RESULTS AND DISCUSSION

Laterality: Of these patients, 59 (59%) had bilateral exfoliation and 41 (41%) had unilateral exfoliation. Thus totally 159 eyes of 100 Patients had exfoliation. In unilateral cases, left eye as more commonly involved. The higher incidence of bilateral exfoliation in this study is in accordance with various other studies. This could be due to the possibility that the unilateral cases invariably become bilateral at a later date. HENDRY *et al* found the probability of exfoliation developing in the fellow eye to be 6.8% after 5 years and 16.8% after 10 years. The 41 patients with unilateral exfoliation have a risk of developing exfoliation in the other eye later. Hence, these patients with unilateral exfoliation are to be followed up.

Table 1: Age* UB Crosstabulation

Age		UB		Total
		Unilateral	Bilateral	
<50%	Count	3	3	6
	%Within UB	7.3%	5.1%	6.0%
>80	Count	2	1	3
	%Within UB	4.9%	1.7%	3.0%
51-60	Count	14	19	33
	%Within UB	34.1%	32.2%	33.0%
61-70	Count	17	21	38
	%Within UB	41.5%	35.6%	38.0%
71-80	Count	5	15	20
	%Within UB	12.2%	25.4%	20.0%
Total	Count	41	59	100
	%Within UB	100.0%	100.0%	100.0%

Chi Square test

	Value	df	Asymp. Sig (2-sided)
Person Chi square	3.382	4	.496
Likelihood Ratio	3.497	4	.478
No of valid cases	100		

4 cell (40.0%) have expected count less than 5 the

The most common age group in both unilateral and bilateral cases was between 61 and 70 years. In bilateral cases the next common age group was 51 and 60 years followed by 71-80 years, with a similar incidence in the unilateral cases also. Patients with bilateral involvement, on an average were only slightly older than those with unilateral involvement. The differences should be greater if exfoliation commonly occurs in one eye long before the fellow eye. However, the absence of much difference in the mean age of the two groups can be explained by the possibility that the onset of exfoliation was bilateral in

some cases and unilateral in others. Probably we need more sample size to make it statistically significant.

Sex: Of 100 patients⁸ with exfoliation, 73% were males and only 27% were females. In both unilateral and bilateral exfoliation groups, there was a male preponderance. TAYLOR 1980 AND RESNIKOFF *et al* BJO 1991 suggested that exfoliation syndrome could be related to environmental factor, ultra-violet light and hence the male preponderance in the study can be explained to some extent by the fact that in India males are more likely to have outdoor activities than females. In both groups with and without glaucoma males were predominant. Reports in literature according to MADDEN *et al* in 1982, LAMBA and GIRIDHAR JIPMER and SANDERS 1988, reported a definite male preponderance with incidence similar to this study. However, in the group of exfoliation and glaucoma, most of the studies favour no sex predilection.

Glaucoma Association

Table 3:

Sex	Exfoliation without Glaucoma		Exfoliation with Glaucoma		Total	
	No	%	No	%	No	%
Males	15	65.21	58	75.32	73	73
Females	8	34.78	19	24.67	27	27
Total	23	100	77	100	100	100

77% of patients had glaucoma while the 23% had no glaucoma. Thus, there is a definite association of glaucoma in exfoliation syndrome. The incidence of glaucoma in exfoliation syndrome vary from 20-85% in the literature.

Type of Glaucoma

Table 4:

Types of Glaucoma	No	%
Open Angle Glaucoma	56	72.72
Angle Closure Glaucoma	21	27.27
Total	77	100

Thus, open angle glaucoma is more commonly associated in exfoliation syndrome. All these cases were considered to be secondary to exfoliation syndrome. Few authors however question the existence of secondary open angle glaucoma due to exfoliation and favour the theory of POAG with coincidental finding of exfoliation. However recent studies, on the basis of certain clinical and pathological observation, have clearly differentiated the two entities.

Table 5:

Open Angle Glaucoma	Unilateral	Bilateral	Total
	18	38	56

Unilateral open angle glaucoma: Out of the 18 with unilateral⁹ open angle glaucoma 6 had exfoliation in both eyes. In other words, 6 had exfoliation in both eyes, but glaucoma in only one eye. These are the patients that really require regular follow up and periodical evaluation, as there is always a high risk of developing glaucoma in the other eye also. A study by HENDRY *et al* 1987 in the context, has shown that the possibility of the other eye developing glaucoma to be 5.3% ± 0.1% after 5 years and 15.4% ± 2% after 10 years.

Bilateral open Angle Glaucoma: Out of the 38 Patients with bilateral open angle glaucoma¹⁰, 29 had exfoliation in both eyes while 9 had exfoliation in only one eye. Thus 9 patients with unilateral exfoliation, had glaucoma not only in the affected eye, but also in the clinically uninvolved eye. It is in this context, once again, the doubt of glaucoma being secondary to exfoliation or a primary glaucoma arises. PRINCE and SPEAKMAN have proved Conjunctival biopsy of the uninvolved eyes is invariably positive for exfoliation material. MIZUNO showed that cycloscopic examination of the fellow eyes showed evidence of exfoliation material on zonules and ciliary processes. Thus clinically uninvolved fellow eyes might have exfoliation material evidence by conjunctival biopsy and cycloscopy but not detected by routine slit-lamp examination.

Table 6: Angle closure glaucoma

Angle closure Glaucoma	Unilateral	Bilateral	Total
	14	7	21

Table 7:

Angle Closure Glaucoma	Primary Angle closure Glaucoma	Secondary Angle closure Glaucoma	Total
		Subluxated lens	7
		Intumescent lens-	3
		Ch Iridocyclitis-	4
	7	14	21

7 patients had secondary angle closure glaucoma due to subluxated lens. All the patients had immature cortical cataract and there was no history of trauma¹¹ in them. Thus, the subluxation¹² evidenced by Phakodonesis and iridodonesis is due to the exfoliation material causing weakness of zonules and hence exfoliation can be attribute as the cause for angle closure glaucoma. In 7 patients there was no other secondary factor involved except for the presence of exfoliation. The fellow eyes also had shallow anterior chamber. These patients are likely to have primary angle closure glaucoma with coexisting exfoliation, as angle closure glaucoma with exfoliation syndrome has been considered rare and only coincidental. A study by EPSTEIN *et al* 1994 has also highlighted the increased incidence of angle closure glaucoma in exfoliation syndromes¹³ than previously thought. Our other observations¹⁴ in this study are 10

patients had Pterygium. Spheroidal degeneration was present in 3 patients with exfoliation. The associated occurrence of these feature¹⁵ has been reported by TAYLOR and RESNIKOFF, suggesting a common aetiology of ultraviolet light. 54% of exfoliation eyes had nuclear cataract, while 31.44% had cortical cataract. The increased incidence of nuclear cataract in exfoliation eyes found in this study is in accordance with similar reports from other studies¹⁶ (SELAND 1982, SOOD 1971). 7 cases had subluxated lens causing angle closure glaucoma. This suggested zonular weakness and a cautions surgery and capsulotomy is warranted. On Gonioscopy almost all cases had increased trabecular pigmentation. It was also seen in the uninvolved fellow eye of unilateral cases and the pigmentation was more on the eye with raised tension in bilateral cases. The trabecular hyper pigmentation¹⁷ of the fellow eye in Unilateral cases could be a preclinical sign of exfoliation syndrome. Pseudo exfoliation material was seen in the angle in 4 eyes. 71 patients had IOP more than 21 mm of Hg.

Assessment Of Blood Aqueous Barrier: Aqueous protein estimation

Table 8: T Test Group Statics

CE	N	Mean	Std. Deviation	Std. Error Mean
Control	25	.2992	.06763	.01353
Exfoliation	25	.5624	.11425	.02285

Table 8b: Independent sample test

		Equality of Variances		t-test for equality of means						
		F	Sig	T	Df	Sig (2-tailed)	Mean difference	Std. Error difference	Of the differences	
									Lower	Upper
Values	Equal variances assumed	7.17	.010	-9.912	48	.000	-.26320	.02665	-.31659	-.20981
	Equal variances not assumed			-9.912	38.982	.000	-.26320	.02665	-.31691	-.20949

Thus aqueous protein concentration in this study group is definitely higher than in control eyes. As described earlier the increase in protein concentration is a definite indicator of the impairment of blood aqueous barrier. KUCHLE *et al* have also done similar study to assess the blood aqueous barrier. In their study, the mean aqueous protein concentration in exfoliation eyes and no exfoliation eyes were 0.56mg/ml and 0.30 mg/ml respectively. This data is statistically very significant with this minimal sample size hence it should be considered has important pathognomonic feature of pseudoexfoliation syndrome. The rise in total protein concentration in exfoliation eyes in this study when compared to KUCHLE'S study could be attributed to the difference in races of the study patients, one being that of Asian race (this study) and

other German race (Kuchl's study) The impairment of blood aqueous barrier was also clinically correlated with the presence of flare in most of the patients. KUCHLE has also quantified flare using laser flare cell meter and found it to be higher in exfoliation syndrome. The impairment of blood aqueous barrier is potentially attributed to "iris vasculopathy", usually associated with exfoliation¹⁸. The blood aqueous barrier breakdown is likely to be aggravated in the postoperative period in these patients, leading to early or late postoperative complications.

Iris Fluorescen Angiogram: Iris fluorescein angiogram was done at random in 10 patients with exfoliation and 5 without it, in the similar age group for control. All patients with exfoliation syndrome showed intense peri-pupillary leakage, even in early cases. The pupillary

leakage was seen as small tufts of hyper fluorescence at the pupillary border that enlarged, coalesced and showed progressively diffuse border as the fluorescence increased. The late angiogram showed intense diffusion of the dye into anterior chamber. In the control eyes, there was no leakage of dye. Although mild pupillary leakage normally occur in 20% of older individuals The great amount of dye leakage and intense diffusion into the anterior chamber in late phase seen in exfoliation eyes, is a definite indicator of alteration of blood aqueous barrier. A similar observation of increased leakage has been observed by BROOKS 1987 and further substantiated with fluorophotometry by JOHNSON 1982. These exfoliation eyes showing increased peri-pupillary leakage, are more prone for increased postoperative complications, especially uveitis. Hence iris fluorescein angiogram can be used preoperatively to assess the severity of blood aqueous barrier impairment. Hence in exfoliation eyes preoperative steroids¹⁹ or NSAID can be used to reduce the complication rate. RAVALICO²⁰ *et al* 1994 suggested the use of Heparin surface modified intraocular lens implantation in eyes with exfoliation syndrome, to reduce the postoperative anterior segment inflammation.

Electron Microscopic Study: Ultra-structural studies were done on lens capsule and trabecular meshwork or pseudo exfoliations eyes. Both of them showed similar morphology in regard to exfoliation material. The exfoliation material appeared as granular, rod like disorderly fragmented structure of 30-50 nm size. Most of the exfoliation material was seen outside the basement membrane and similar amorphous material was seen in between the collagen bundles also. The collagen also showed degeneration by way of fragmentation and attained granular morphology, giving the resemblance to exfoliation material seen around the basement membrane. In some place, the basement showed duplication and the exfoliation material was discernible in between the layers of basement membrane. The presence of exfoliation material²¹ on the surface and between the layers of the basement membrane favours the genesis of exfoliation material, being due to the degeneration of basement membrane. Similar observation of exfoliation material in association with basement membrane has been reported in literature. It is in this context that EAGLE *et al* proposed the term basement membrane exfoliation syndrome. However, the presence of similar material between the bundles of collagen could suggest the possibility of exfoliation material, being a degenerative product of collagen. But, this can be confirmed only by immune electron microscopic analysis, by differentiating the type of collagen involved.

CONCLUSION

Bilateral exfoliation was more common than unilateral exfoliation. The maximal incidence of exfoliation²² in both unilateral and bilateral cases was in the age group of 61-70 years, with a mean age if 64.5 years. Exfoliation syndrome²³, though a disease of the elderly can occur in less than 50 years age group. The youngest patient reported in this study was a 46-year-old female. In all groups of exfoliations patients²⁴, with or without glaucoma, and both unilateral and bilateral, Males predominated.

Glaucoma: Exfoliation syndrome is definitely a risk factor for the development of glaucoma²⁵. Exfoliation is more commonly associated with open angle glaucoma, but may predispose to angle closure glaucoma also. Nuclear cataract has a more common incidence when compared to cortical cataract in eyes with exfoliation. In unilateral cases, the clinically uninvolved fellow eye²⁶ also has a risk of developing glaucoma. Nuclear cataract in exfoliation eyes is commonly associated with open angle glaucoma²⁷. Cortical cataract in exfoliation eyes is commonly associated with angle closure glaucoma.

Blood Aqueous Barrier: The impairment of blood aqueous barrier in exfoliation syndrome²⁸ is evidenced by the rise in mean aqueous protein concentration estimation by biochemical methods. Intense peripupillary leakage of dye seen with iris fluoresce in angiography. Preoperative evaluation²⁹ for assessing the severity of blood aqueous breakdown can be done by iris fluoresce in angiography.

Electron Microscopic Study: Ultra structural studies show exfoliation material as granular, rod like fragmented structures measuring 30-50 nm. Exfoliation syndrome is probably a basement membrane disorder³⁰, as evidenced by "Duplication of basement membrane and intimate association of exfoliation material with basement membrane". Pseudo exfoliation syndrome has a great set of risks and challenges for cataract surgeons. We shall minimize and often prevent complications by meticulous pre-operative evaluation and cautious surgical techniques.

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