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Original Research Article

Association between ocular pseudoexfoliation and cardiovascular disease status: An analysis in a multi-speciality Hospital

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ABSTRACT

Background: Pseudoexfoliation syndrome (PEX) is the most common cause of secondary open angle glaucoma. It is a systemic disorder characterized by extracellular deposition of distinctive grey-white fibrillary amyloid like material. The material is found in the anterior segment of the eye, where it can be easily identified on ocular (slit- lamp) examination by ophthalmologists. This study was carried out to determine if an association does exist between ocular pseudoexfoliation and cardiovascular disease.

Materials and Methods: This was a cross-sectional case-control study carried out from March 2023 to June 2023 at a tertiary hospital. A total of 46 cases (patients with ocular pseudoexfoliation) and 46 controls (patients without ocular pseudoexfoliation) were randomly selected from Ophthalmology Outpatient Department. Ophthalmological examination was done which included visual acuity testing using standard Snellen's Chart, anterior segment assessment by slit lamp examination, Goldmann Applanation Tonometry to check intraocular pressure (IOP) and dilated fundus examination by direct/indirect ophthalmoscopy. Blood pressure (BP) was assessed and Electrocardiogram (ECG) was performed for all the patients undergoing the study. 2D Echocardiogram (ECHO) was done if ECG was abnormal.

Results: Analysis of the study results showed a positive association between ocular pseudoexfoliation and hypertension (HTN) and abnormal ECG. Also, the condition appeared to be more prevalent among the males.

Conclusion: Since there is a positive association between pseudoexfoliation and cardiovascular diseases (CVD), ophthalmologists need to proactively investigate patients with PEX for cardiovascular abnormalities in form of HTN and abnormal ECG and refer them to physicians for appropriate management, if necessary.

1. Introduction

The presence of pseudoexfoliative (PXF) material in the eye is called 'pseudoexfoliation syndrome'(PEX). It is an important cause for secondary open angle glaucoma. It is rare before 50 years of age and more common in women than men. It is a systemic disorder characterized by extracellular deposition of distinctive grey-white fibrillary amyloid like material. The exfoliative material is composed of abnormal cross-linked fibrils that accumulate progressively in some organs. The exact pathophysiology of this condition is not fully clear, certain genetic and environmental factors are believed to have a role in the development and progressive deposition of this material. LOXL1 gene polymorphisms and increased exposure to UV rays in atmosphere may be associated with PEX.[1] The material is found in the anterior segment of the eye - on the lens epithelium and capsule, pupillary margin, ciliary epithelium, zonular fibres, iris pigment epithelium

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and subconjunctival tissue. It is also present in other parts of the body.

Ophthalmological manifestations are usually bilateral but asymmetric and can cause visual difficulty, mainly related to glaucoma and cataract. Pseudoexfoliation glaucoma, a major complication of PEX, is well recognized worldwide. Nuclear cataract occurs more frequently and earlier in this condition. Poor pupillary dilatation and increased zonular instability leads to a greater risk of surgical complications associated with cataract surgery.[1] Open angle glaucoma associated with pseudoexfoliation is due to raised IOP which is caused by trabecular meshwork obstruction by PXF material and liberated iris pigment combined with degenerative outflow dysfunction. This syndrome is associated with increased prevalence of systemic disorders, hearing loss and Alzheimer's disease.

This syndrome is strongly age related- rare in people less than 50 years of age. The classic feature of the disease is the "bull's eye pattern" of the pseudoexfoliative material (Figure 1), possibly caused by iris movement on to the anterior lens capsule. It is seen well with pupillary dilatation on slit lamp examination. Iris may show transillumination defects due to peripupillary atrophy. Poor pupillary dilatation is possibly due to the material infiltrating into the stroma. The IOP elevation associated with this condition is possibly due to the deposition of the fibrillary material in the angle causing obstruction to the outflow pathway of aqueous humor in the anterior chamber of the eye.

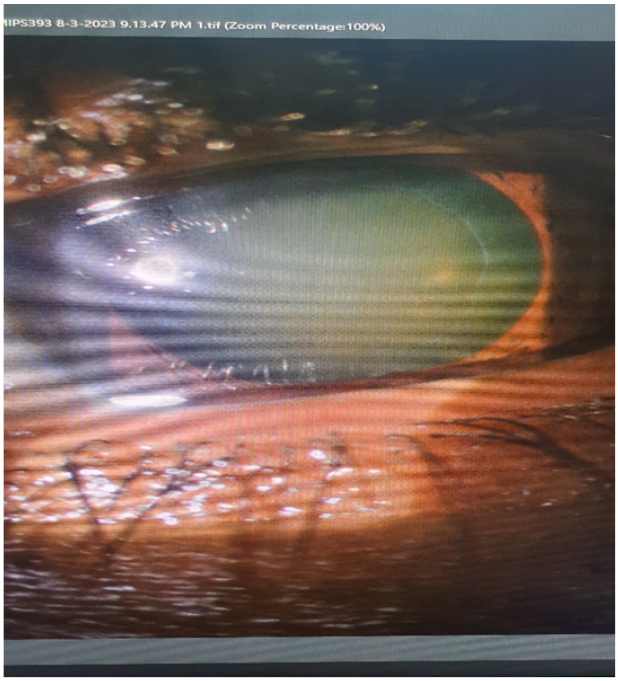

Figure 1: Pseudoexfoliative material on the anterior lens capsule

This condition was first described by John G. Lindberg as a characteristic flaky material noted in eyes of glaucoma patients. In 1950s the term 'pseudoexfoliation' was coined for the same. It has been the subject of increasing research and is now known to be a risk factor for glaucoma and other vision problems. Raised intraocular pressures are seen in around 44% of patients making it an important cause of secondary open angle glaucoma.[2]

Many studies have associated cardiovascular disease with PEX but a definite relationship is yet to be established. In their article 'Ocular Pseudoexfoliation Syndrome Linkage to Cardiovascular Disease', Juan A Siordia et al state that a literature review involving 18 studies showed that cardiovascular disorders that had a statistically significant association (within a 95% confidence interval) with PEX were ischaemic heart disease, aortic aneurysms and homocystinuria.[3]The association between IHD and PEX was statistically significant (p=0.045).[3]

Another study by Dustin D French et al concluded that association of ocular pseudoexfoliation and CVS diseases were less when compared to patients with POAG.[4]

Georgios K Andrikopoulos et al in their study 'Pseudoexfoliation syndrome and cardiovascular diseases', have pointed out that systemic and ocular blood flow changes, increase in vascular resistance, and decrease in blood flow velocity, arterial endothelial dysfunction, arterial hypertension and increased plasma homocysteine have been shown in PEX patients. Some features like oxidative stress and inflammation, which are seen in both atherosclerosis and PEX may suggest that grey-white deposits and cardiovascular disorders are related.[5]

'Ocular pseudoexfoliation syndrome' by Jasmina Dordevic-Jocic noted the presence of systemic associations of cardiovascular, cerebrovascular, abdominal aorta aneurysm with PEX. The syndrome is now known as an elastic microfibrillopathy where TGF-beta, and MMP oxidative stress play a role.[6]

In another study, Uri Aviv et al have reiterated the association of PEX with systemic conditions like increased vascular risk, dementia and inflammatory conditions.[7]

In our study, we screened 46 patients with ocular pseudoexfoliation (cases) for cardiovascular disease and the same number of patients without ocular pseudoexfoliation (controls) for the same in an attempt to find out if there exists any significant association between ocular pseudoexfoliation and cardiovascular disease.

2. Materials and Methods

Nature of study – Cross-sectional case-control study.

The study was carried out from April 2023 to July 2023 in a tertiary multi-speciality in South India. Permission from Institutional Ethics Committee was obtained for the study. A total of 46 cases (patients with ocular pseudoexfoliation) and 46 controls (patients without ocular

pseudoexfoliation), randomly selected from Ophthalmology Outpatient Department were enrolled.

2.1. Inclusion and exclusion criteria

Patients above the age of 21 years, not previously diagnosed with cardiovascular disease, willing to undergo detailed ophthalmological evaluation were included in the study. Exclusion criteria for the study were patients less than 21 years of age, known cardiovascular disease patients, recent ocular surgery and patients with active ocular diseases.

All patients were explained about the study and informed consent was taken from them as verbal or in written format. Detailed clinical history regarding patient's cardiovascular status like dyspnoea, angina, palpitations, effort intolerance and pedal edema was obtained along with history of ocular complaints and documented. Ophthalmological examination included visual acuity testing by the subjective method using standard Snellen Chart according to the international standards. Anterior segment assessment by slit lamp examination, Goldmann Applanation Tonometry to check intraocular pressure (IOP) and fundus examination by direct/indirect ophthalmoscopy after dilatation of the pupil were performed. Blood pressure (BP) was assessed and Electrocardiogram (ECG) was performed for all the patients undergoing the study. 2D Echocardiogram (ECHO) was done if any ECG changes were noted or if any cardiovascular complaints were present.

IOP greater than 21 mmHg, BP > 140/90mmHg were taken as abnormal values for the study.

All data in our study was analysed using the software SPSS version 16. Association between pseudoexfoliation and cardiac risk factors was assessed by Fisher's Exact Test/Chi-square test. A p value of <0.05 was considered as statistically significant.

3. Results and Statistical Analysis

The Table 1 statistical table is derived from data collected by us. In total, 92 patients were enrolled in the study of which 46 were cases (patients with PXF) and 46 were controls (patients without pseudoexfoliation). For total of 92 patients, mean age was 63.21+/- 7.834. Among 46 cases, 31(67.4%) were male and 15(32.6%) were female. Among 46 controls, 19(41.3%) were male and 27(58.7%) were female. There is a positive correlation (p=0.012) between sex and pseudoexfoliation suggesting that male sex is possibly more prone to PXF syndrome.

On fundus examination, CDR >0.5:1, optic atrophy, parapapillary atrophy, retinopathy changes (hypertensive or diabetic) were taken as abnormal fundus. Among PEX cases, 12(26.1%) had abnormal fundus while among the 46 controls, 6(13%) had abnormalities in fundus. The p value was 0.115 suggesting that there was no significant association between the two.

While examining the ECG reports, it was seen that 16(34.8%) cases had abnormal ECG while 30(65.2%) had normal reports. Among non- pseudoexfoliation patients, only 3(6.5%) cases had abnormal ECG while 43(93.5%) had normal reports. The association between abnormal ECG and PEX was significant (p=0.001).

ECG changes noted in the cases were as follows- sinus bradycardia was most common, seen in 7 cases. Other changes seen were slightly peaked T waves in chest leads in 1 case, ST depression in leads V2 and V3 seen in 1 case, T wave inversion in V4, V5, V6, 2,3, AVF in 1 patient, Q waves on V1, V2 in 1 pt, 1^{st} degree heart block in 1 patient, LVH and LV strain pattern in 1 case, LVH with T wave inversion in V4, V5, V6, AVL, P flattening in 1 case, flat T in V2 in 1 case, flat T in lead 3 in 1 case, prolonged QT in 1 case.

The ECG changes noted among the controls were T wave inversion in V1, V4 in 1 patient, ?LVH and T wave inversion in AVL, V2, in 1 patient and sinus bradycardia in 1 patient. (Table 2)

Among 46 PXF patients, 5 (10.9%) patients were diagnosed as diabetes mellitus while 41 patients were nondiabetic. Among controls, the corresponding values were 11(23.9%) and 35(76.1%) respectively. There was no positive association between DM and PEX (p value=0.099).

All patients were screened for hypertension. Among PEX patients, 17(37%) were hypertensive while the remaining 29(63%) did not have HTN. Only 8(17.4%) patients among 46 in the non-pseudoexfoliation group had HTN while 38(82.6%) had normal BP. Association between pseudoexfoliation and hypertension was significant (p value=0.035).

Anaemia was present in 6 or 13% of PEX patients and in 3 or 6.5% of non PEX patients- no significant association noted – p=0.292

No positive correlation noted between PEX and CKD; 2(4.3%) PEX patients had CKD while 44(95.7%) did not. The prevalence of CKD among non PEX patients was exactly the same. P-value was 1(not significant).

4. Discussion

Pseudoexfoliation syndrome is an important cause of ocular morbidity. It causes secondary glaucoma, known as pseudoexfoliative glaucoma, which is an important cause of blindness. The condition tends to complicate cataract surgeries. Corneal endothelium may have flaky deposits, pupil usually doesn't dilate well and some zonular weakness can be anticipated. All these factors can make cataract surgery challenging especially in hard cataracts. There might be increased incidence of complications like rupture of capsular bag, zonular dehiscence and vitreous loss.[2] The grey-white fibrillary material (hallmark of the disease) which is deposited in the lens epithelium and capsule, pupillary margin and ciliary zonules is possibly

Table 1: Results of pseudoexfoliation and cardiovascular disease study

Variables		Patients with PEX N=46	Patients without PEX N=46	(P value)
Sex	Male	31 (67.4%)	19 (41.3%)	0.012*
	Female	15 (32.6%)	27 (58.7%)	
Fundus	Abnormal	12 (26.1%)	6 (13%)	0.115
	Normal	34 (73.9%)	40 (87%)	
ECG	Abnormal	16 (34.8%)	3 (6.5%)	0.001*
	Normal	30 (65.2%)	43 (93.5%)	
Diabetes mellitus	Yes	5 (10.9%)	11 (23.9%)	0.099
	No	41 (89.1%)	35 (76.1%)	
Hypertension	Yes	17 (37%)	8 (17.4%)	0.035*
	No	29 (63%)	38 (82.6%)	
Anaemia	Yes	6 (13%)	3 (6.5%)	0.292
	No	40 (87%)	43 (93.5%)	
CKD	Yes	2 (4.3%)	2 (4.3%)	1.0
	No	44 (95.7%)	44 (95.7%)	

*P value- significant, PEX- Pseudoexfoliation

Table 2: The different ECG changes present in cases and controls

ECG Changes Noted	Number of Cases	Number of Controls
Sinus bradycardia (SB)	7	1
T wave inversion in V4, V5, V6,2,3, AVF	1	1 (inversion in V1, V4 only)
Q waves on V1, V2	1	0
1st degree heart block	1	0
LVH and LV strain pattern	1	1 (?LVH with T wave inversion in AVL, V2)
Flat T wave in V2	1	0
Flat T wave in lead 3	1	0
Prolonged QT	1	0
LVH with T wave inversion in V4, V5,V6,AVL,P flattening	1	0
ST Depression in V2, V3	1	0

the cause for the above scenario. Several studies have demonstrated the association of pseudoexfoliation with systemic diseases.[6,7] The presence of the characteristic flaky material in extraocular tissues like skin, heart, lung and liver possibly contributes to its cardiovascular, cerebrovascular and other systemic manifestations.

A collaborative case-control study 'A possible link between pseudoexfoliation syndrome and coronary artery disease' by M Citirik et al showed statistically significant difference in the prevalence of PEX among patients with Coronary artery disease(CAD) and also in the presence of CAD in PEX patients.[8]

A sample size of 60 (30 pseudoexfoliation cases and 30 controls) was calculated from this article by M Citirik et al[8] in which the proportion of CAD among ocular pseudoexfoliation patients was 70% and the proportion of CAD among people without ocular pseudoexfoliation was 20%. Estimated risk difference was found to be 50%. To detect this difference, the sample size was calculated with an alpha error of 5% and power of 95%.

As mentioned, we screened 46 patients with ocular pseudoexfoliation (cases) for cardiovascular disease and the same number of patients
without ocular pseudoexfoliation (controls) for the same in an attempt to find out if any significant association exists between ocular pseudoexfoliation and cardiovascular disease.

A multicentre study by Ugne Rumelaitiene et al demonstrated that over a period of 10 years, prevalence of PEX in study population increased from 10.3 to 34.2%. The rates of ischaemic heart disease (IHD) and IHD combined with stroke were higher in PEX subjects than in non-PEX subjects.[9]

A population based randomized trial in Turkey showed 5% prevalence of PXF in patients more than 40 years of age. It further demonstrated that PEX was associated with hypertension, hearing loss and using drugs for cardiac and psychiatric diseases, in addition to cataract and glaucoma.[10]

Another study by a tertiary eye hospital in South India showed PEX was associated with higher systolic BP and more frequent ECG abnormalities. Hence, cardiac

morbidity may be higher in these patients.[11] A study by Caleb Shumway et al concluded that patients with obstructive sleep apnoea may be at an increased risk of exfoliation syndrome compared to patients without the above condition, especially in those with a history of HTN.[12]

The review article, 'Pseudoexfoliation Glaucoma: Clinical Presentation and Therapeutic Options' by N Yuksel et al[13] reports several cardiovascular and cerebrovascular associations of PEX, which include history of angina pectoris, systemic hypertension, stroke, asymptomatic myocardial dysfunction, transient ischaemic attacks, Alzheimer's disease and neurosensory hearing loss.[14–16]

Another study (review article) also mentions about the predisposition to various spontaneous and surgical ocular complications in this condition.[17]

Hence, pseudoexfoliation does not seem to be a benign entity. In view of its widespread clinical implications, the condition has been studied extensively.[18] However, the exact cause is not known and further research needs to be done.

In our study, patients with ocular pseudoexfoliation had positive association with abnormal ECG(p=0.001) implying that people with this condition are more prone to have abnormal ECG than people without pseudoexfoliation (Figure 2). Moreover, in our study, hypertension was also positively associated with PEX(p=0.035), which means that patients with pseudoexfoliation are more likely to be hypertensive than those without this condition. We also found a positive correlation between male gender and pseudoexfoliation (p=0.012), which suggests that males are more likely to have this condition than females.

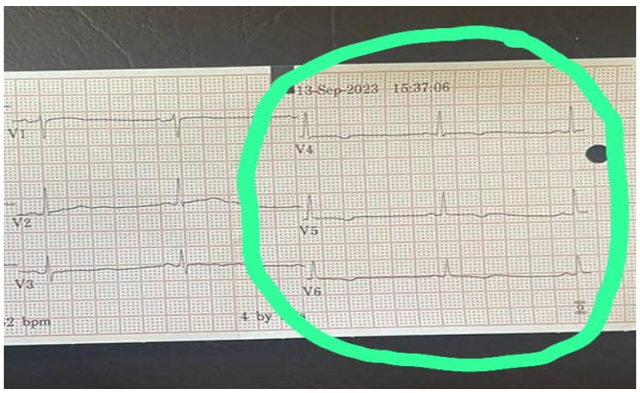

Figure 2: Abnormal ECG tracing of a patient with pseudoexfoliation syndrome showing T wave inversion in leads V4, V5 and V6

5. Conclusion

In conclusion, pseudoexfoliation is an age related and stress related extracellular fibrotic matrix disorder with fibrillar deposits in various tissues. These patients are prone to develop glaucoma and also appear to have a higher risk of cardiovascular and cerebrovascular diseases. Our study done has shown a positive correlation of ocular pseudoexfoliation with abnormal ECG findings (p value=0.001) suggesting a significant association between the condition and cardiovascular morbidity. As elaborated above, while some ECG changes like sinus bradycardia may be physiological, others like ST depression in selected leads and T wave inversion may be harbingers of serious cardiac diseases like ischaemia or unstable angina. Such cases need to be evaluated in detail by physicians with ECHO and/or cardiac enzyme study, as required. Our study has also demonstrated a positive association between pseudoexfoliation and hypertension (p value=0.035), which again strengthens the association with underlying cardiovascular morbidity. Hence, patients with pseudoexfoliation should be monitored and evaluated carefully for associated systemic abnormalities. Referral to physicians to be advised whenever indicated.

Ophthalmologists have always been wary of pseudoexfoliation syndrome in patients being evaluated for cataract surgery as the condition is known to predispose the patients to quite a few intraoperative complications. Now, their responsibility with regard to these patients has increased. They will have to play an important role in screening patients diagnosed to have ocular pseudoexfoliation disorder on routine slit lamp examination for cardiovascular morbidity. Needless to say, further research needs to be done on the manifold systemic implications of pseudoexfoliation syndrome.

6. Source of Funding

None.

7. Conflict of Interest

None.

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