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RESEARCH ARTICLE

OCULAR CLINICAL PROFILE OF PATIENTS WITH PSEUDOEXFOLIATION SYNDROME AND PSEUDOEXFOLIATION GLAUCOMA AT TERTIARY CARE CENTRE IN KASHMIR

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Abstract

Aim: To study the clinical profile of pseudoexfoliation (PEX) syndrome and Pseudoexfoliation glaucoma at tertiary care centre in Kashmir.

Materials and Methods: A cross sectional study consisting of 100 PEX and 100 PEXG patiens, attending the general ophthalmology clinic of a tertiary care center in kashmir. All patients underwent a complete ophthalmologic evaluation including recording IOP,gonioscopy and Central Corneal Thickness(CCT).

Results: The study cohort comprised 200 patients(100 with PEX and 100 with PEXG). There were 145(72.5) males and 55(27.5%) females. The highest number of patients (120 patients) were from the age group between 61 and 70years. 145(72.5%) patients were involved in outdoor activities.153(76.5%) patients had bilateral involvement of pseudoexfoliationand pseudoexfoliative material was present at anterior lens capsule in 175(49.58%) eyes. Nuclear cataract was predominant type of cataract and was present in 188(48.2%)eyes. Mean IOP was 17.26±7.634mmHg in PEX group and 24.39±4.456mmHg in PEXG group. Gonioscopyshowed open angles in 96.5% of eyes and occludable in 3.5% eyes . Mean central corneal thickness was 531.80±19.127µm.

Conclusion: The prevalence of PEX is found to increase with age. Patients with PXG had more severity of optic nerve damage at presentation. Therefore a careful assessment for detection of PEX is warranted and regular follow-up of patients is desired to minimize the extent of optic nerve damage.

Introduction:-

Pseudoexfoliation syndrome (PEX) was initially described by a Finnish ophthalmologist, John Lindberg in 1917[1].It represents a common age related systemic disorder affecting approximately 10% to 20% of the general population over age 60 and involving both genetic and nongenetic factors in its etiopathogenesis[2,3]. It is characterised by pathologic accumulation of an abnormal fibrillar extracellular material in the anterior segment of the eye and in various extraocular tissues[4]. Progressive obstruction of the aqueous humor outflow pathways by abnormal pseudoexfoliation material deposits cause chronic pressure elevation, optic nerve damage and subsequent development of open angle glaucoma in eyes with PEX syndrome, a condition known as pseudoexfoliation glaucoma(PEXG)[5]. It accounts for a majority of glaucoma cases in some countries and for approximately 25% of

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open angle glaucoma worldwide[6]. Based on systemic nature of underlying connective tissue disorder PEX syndrome has been associated not only with glaucoma but also a broad spectrum of other ocular, surgical and systemic complications including cardiovascular and cerebrovascular disease[7-9].

Pex And Epidemiology:
Despite its worldwide distribution, there is a clear tendency for PEX syndrome to cluster geographically and in certain racial or ethnic subgroups. In people aged 60 years or older, PEX syndrome has been reported to be more common in the Caucasian population with the prevalence of 10% to 20% in Northern Europeans[10,11], when compared with the Asian population with the prevalence of 0.4% in Hong Kong Chinese, 0.7% in Singaporean, and 2.4% in Japanese[12-14].Studies on PEX syndrome have resulted in contradictory results regarding gender. For example, PEX syndrome is more common in women than in men in Sweden, Iceland and in the USA, but in India and Burma there are no difference regarding gender[15-19]. The incidence for PEX syndrome increases with advancing age. In Indian population the prevalence of PEX syndrome has been reported to vary from 0.69%-3.8%[18,20]. Studies conducted on Kashmiri population have found the prevalence of PEX syndrome to be 26.32%[21] and that of PEXG to be 38.3%[22].

Clinical manifestations
Ocular:

Glaucoma:
Pseudoexfoliative material can be observed in most cases on the pupillary margin and on the anterior lens capsule. PEX is considered to be one of the most common causes of secondary open-angle glaucoma or ocular hypertension and early cataract development, because of its characteristics, including poor and impaired pupillary dilation, posterior synechiae, subluxation or dislocation of the lens and presence of weakened zonules[23]. It has been suggested that PEXG may be due to the congestion of the trabecular meshwork[24].

PEXG is mostly bilateral and asymmetric; if compared to primary open angle glaucoma it presents a worse prognosis due to higher fluctuations in IOP levels and more severe optic nerve and visual field damage in affected eyes. Furthermore patients with PEXG usually present higher levels of IOP compared to those affected by POAG; moreover, various studies report a higher percentage of failure of medical management (prostaglandins, beta-blockers, adrenergic agonists, and carbonic anhydrase inhibitors) for PEXG patients.

Lens:
PEX is usually diagnosed by slit lamp examination that allows observing accumulation of whitish material deposits on the lens capsule. The typical bull's eye pattern disposition is probably due to the movement of the iris on the anterior lens surface, creating a double concentric ring aspect. Therefore, it is important to examine the anterior capsule of the lens after pupillary dilation, and in most cases the presence of three different areas is observed[25].

It has been observed that patients with PEX present a higher percentage of nuclear cataract[26].Cataract development seems to be related to the age of patients, although, in patients with unilateral PEX, cataract appears to be more advanced on the affected rather than the unaffected eye.

Cornea:
Slit lamp examination may demonstrate the presence of pseudoexfoliative material and pigment on the corneal endothelium that can be erroneously interpreted as inflammatory precipitates[27]. Confocal microscopy has demonstrated the presence of a lower number of endothelial cells in affected eyes and a consequent higher rate of guttae, which may probably be due to intermittent elevated levels of IOP.

Other non specific changes of the corneal endothelial cells include rarefaction and thinning of the cells, cytoplasmic vacuolization, phagocytosis of melanin granules, and abnormal extracellular matrix production.

Aqueous Humor and Anterior Chamber:
Aqueous humor production in PEX affected eyes has been demonstrated to be reduced and associated with a disrupted blood-aqueous barrier with a consequent presence of higher levels of aqueous protein concentration, as well as sudden changes in levels of acid phosphatase, alpha1-lipoprotein and ceruloplasmin, cellular/plasma fibronectin, transferrin, alpha1-antitrypsin, and growth factors.

Iris:
Presence of pseudoexfoliative material is frequently observed on the anterior and posterior surface of the iris[28].Irregular borders, due to the rubbing of iris against the lens and presence of grayish material deposits, characterize the aspect of pupil margin in PEX. In most cases this is associated with poor or absent pupillary dilation as a result of atrophic and/or fibrotic changes in the iris sphincter muscle. Recent studies described various cases presenting iris ischemia and neovascularization, as a consequence of the deposition of pseudoexfoliative material on the vascular endothelium of the iris.

Zonules and Ciliary Body:
Weakness of the zonules is one of the main aspects of PEX representing an important cause of complication during cataract surgery. It is thought that this zonular fragility can be caused by accumulation of pseudoexfoliative material on the ciliary processes and zonules, which may lead to phacodonesis[29].

Angle:
Gonioscopy represents one of the fundamental examinations, which should be performed in patients with PEX. Changes in both the aspect and depth of the angle commonly occur in PEXG affected patients. Pigment and flecks of pseudoexfoliative material can be observed over the structures of the angle, especially along the Schwalbe line, where the pigment dispersion pattern is named "Sampaolesi's line"[30].

Patients And Methods:-

This cross sectional study was conducted at postgraduate Department of Ophthalmology Government Medical College Srinagar, after obtaining clearance from the institutional ethical committee from October 2018 to October 2020 over a period of two years. A total of 200 patients were included in the study. These include 100 patients with pseudoexfoliation syndrome (PEX) and 100 with pseudoexfoliation glaucoma(PEXG).

PEX: these patients exhibited deposits of exfoliative material on the anterior lens capsule and/or iris during slit lamp examination, in one or both eyes
PEXG: in addition to exfoliative material these patients showed the characteristic optic disc damage

Exclusion Criteria:
Non kashmiri
Patients <50 years of age
History of ophthalmic medication.
Previous intraocular surgery / trauma/ laser
Secondary cataract
Uveitis.
Primary open / closed angle glaucoma
Other secondary glaucoma
Systemic Conditions such as Diabetes.
Prior to clinical examination, a questionnaire was administered including demographic data, ophthalmologic, and medical history. In particular, subjects were queried whether they had ever been diagnosed with hypertension, diabetes mellitus, any cardiovascular disease.

Examination
Comprehensive ocular examination was performed for all eligible candidates which included the following parameters:
1.Visual acuity test was performed at a distance of 6 meters using Snellen's or illiterate E charts. The lowest line read successfully was taken as the visual acuity for the eye.
2. Refraction/ retinoscopy(using Heine Beta 200 streak retinocope).
3. Intra ocular pressure was measured using Goldman applanation tonometer.
4. Gonioscopy was performed with a two-mirror lens and the angle was graded according to Shaffer system as:

- Grade 0: Closed angle, no angle structures visualized
- Grade 1: Very narrow angle, only Schwalbe's line visible
- Grade 2: Moderately arrow angle, up to TM visible
- Grade 3: Open angle, up to scleral spur identified
- Grade 4: Wide open, all structures up to ciliary body identified.

If the patient could not cooperate for gonioscopy, the van Herick technique was used to grade the peripheral anterior chamber depth with the slit lamp. If the peripheral chamber was less than one fourth of corneal thickness, the angle was considered occludable, otherwise it was considered open.

5. Detailed slit lamp examination was done and following signs were looked for

Conjunctiva- congestion

Cornea- edema, pigmentation, exfoliation material

Anterior chamber- depth, flare, cells, depth, exfoliation material, pigment dispersion

Iris- pattern, transillumination defects, iridodonesis

Pupil- size, reaction to light, exfoliation material.

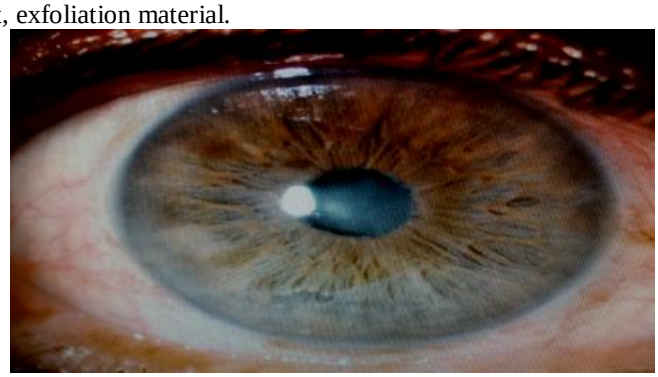

Figure 1:- Showing pseudoexfoliative material on pupillary margin.

Pupil was dilated, unless contraindicated because of the risk of angle closure, to note the three zones of exfoliation material on the lens capsule.

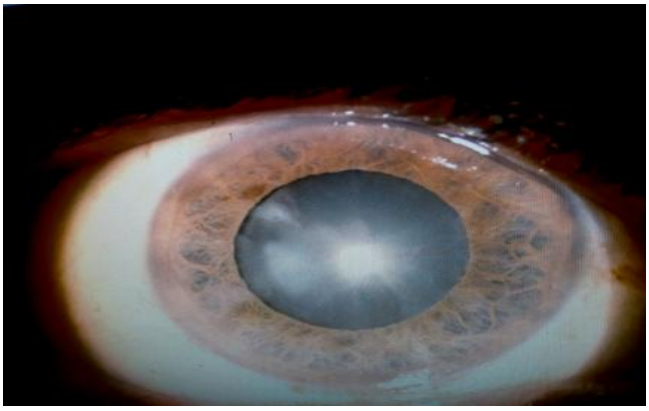

Figure 2:- showing poor pupillary dilatation in PEX patient.

Lens- exfoliation material, cataractous or not, phacodonesis, subluxation or dislocation of lens. Cataracts were classified morphologically as nuclear sclerosis(NS), cortical and posterior subcapsular(PSC).

6. Stereoscopic examination of the optic disc and peripapillary area was performed at the slit lamp using a 78-D lens. The following disc features evoked suspicion of glaucomatous damage:

- vertical cup disc ratio (CDR >0.5) in either eye
- asymmetry of CDR > 0.2 between the two eyes
- thin or notched neuroretinal rim, or disc hemorrhage
- nerve fiber layer defect with the corresponding characteristic changes in the visual field.

7. Measurements of the central corneal thickness (CCT) was performed on each eye using specular microscope(Topcon SP-1P,Tokyo,Japan).

Statistical analysis

Data was entered in Microsoft Excel 2010 and analyzed by using SPSS version 23. Categorical variables were summarized as frequencies and percentages whereas, continuous variables were summarized as mean and standard deviation. We used logistic regression for calculating odds ratio. Chi-square test and t-test were used wherever appropriate. P value<0.05 was considered statistically significant.

Results:-

The present study was conducted in the Department of Ophthalmology, Government Medical College, Srinagar from October 2018 to October 2020.This was a cross sectional study in which 200 patients were included (100 with PEX and 100 with PEXG). The mean age in PEX group was 62.98 ± 6.664years and majority of patients were in the age group of 60 to 70 years , whereas the mean age in PEXG group was 65.32± 6.628years and majority of patients were in the age group of 60 -70 years . Distribution of age is given in table 1 and 2.

Table 1:-

Age group (in years)	PEX	PEXG
	Number (%)	Number (%)
50-60	27(27)	20(20)
61-70	58(58)	62(62)
71-80	15(15)	18(18)
Total	100(100)	100(100)

Table 2:-

	Subjects	Number	Mean	Standard Deviation
Age	PEX	100	62.98	6.664
	PEXG	100	65.32	6.628

Majority of the patients were males in both groups. Descriptive data regarding gender distribution is given in table 3:

Table 3:-

Gender	PEX	PEXG
	Number(%)	Number (%)
Male	74(74)	71(71)
Female	26(26)	29(29)
Total	100(100)	100(100)

Most of the patients were involved in outdoor activities in both groups and mostly were from rural areas in both PEX and PEXG groups as shown in table 4 and 5.

Table 4:- showing activity of subjects.

Activity	PEX	PEXG
	Number(%)	Number(%)
Outdoor	74(74)	71(71)
Indoor	26(26)	29(29)
Total	100(100)	100(100)

Table 5:- Showing residence of subjects.

Residence	PEX	PEXG
	Number(%)	Number(%)
Rural	68(68)	72(72)
Urban	32(32)	28(28)
Total	100(100)	100(100)

Bilateral involvement was in majority of patients in both PEX(73 patients) and PEXG(80 patients) groups.In PEXG group glaucoma was present bilaterally in 72% of patients. Table 6 shows laterality of pseudoexfoliative material in patients and table 7 shows laterality of glaucoma in PEXG patients.

Table 6:- showing laterality of pseudoexfoliative material.

Laterality of pseudoexfoliative material	PEX	PEXG
	Number(%)	Number(%)
Unilateral	27(27)	20(20)
Bilateral	73(73)	80(80)

Total	100(100)	100(100)

Table 7:- Showing laterality of glaucoma in PEXG patients.

Laterality of glaucoma	PEXG
	Number(%)
Unilateral	24(24)
Bilateral	76(76)
Total	100(100)

Regarding site of exfoliation , deposition of material at anterior lens capsule was predominant in both PEX and PEXG group, followed by pupillary border. Descriptive data regarding site of exfoliation is given in table 8:

Table 8:- showing site of exfoliation.

Site of exfoliation	PEX Number of eyes(%)	PEXG Number of eyes(%)
Pupillary Border	60(34.68)	65(36.11)
Anerior Lens capsule	80(46.24)	95(52.78)
Both	33(18.44)	20(11.11)
Total	173(100)	180(100)

In the present study most of the patients had visual acuity of less than 6/60 in both PEX and PEXG groups and nuclear type of cataract was common in both groups. The descriptive data regarding visual acuity and type of cataract is given in table 9 and table 10:

Table 9:- Showing visual Acuityof subjects.

Visual Acuity	PEX	PEXG
	Number of eyes(%)	Number of eyes(%)
6/6-6/18	30(15)	26(13)
6/18-6/60	60(30)	52(26)
<6/60	110(55)	122(61)
Total	200(100)	200(100)

Table 10:- showing type of cataract of subjects.

Type of cataract	PEX	PEXG
	Number of eyes(%)	Number of eyes(%)
Nuclear	90(50)	98(49)
Posterior subcapsular	46(25.56)	48(24)
Cortical	44(24.44)	54(27)
Total	180(100)	200(100)

Mean IOP in PEX group was 17.26±7.634mmHg and in PEXG group it was 24.39±4.456mmHg due to presence of glaucoma in such patients. This was statistically significant(p value<0.001) as shown in table 11.

Table 11:- Showing IOP of two groups.

Group	Number	Mean	Standard Deviation	P value
PEX	100	17.26	7.634	0.001
PEXG	100	24.39	4.456	

Table11:- showing mean Central Corneal Thickness(CCT) of two groups.

Group	Mean(CCT)	Standard Deviation
PEX	538	12.124
PEXG	525	13.534

In our study no glaucomatous damage was seen in PEX group and 30 (15%) eyes in the PEXG group. However, early glaucomatous changes was seen in 130(65%) eyes and advanced glaucomatous damage in 40(20%) eyes in the PEXG group.

Table 12:- showing Cup Disc Ratio (CDR) of subjects.

Fundus (CDR)	PEX	PEXG
	Number of eyes(%)	Number of eyes(%)
Normal	200(100)	30(15)
Cupping(0.4-0.8)	0	130(65)
GOA	0	40(20)
Total	200(100)	200(100)

GOA=Glaucomatous Optic Atrophy

Discussion:-

This study was conducted in Department of Ophthalmology, Government Medical College Srinagar from October 2018 to October 2020. The study included 200 subjects who attended the OPD of Department of Ophthalmology. The subjects were categorized into wo groups (100PEX and 100PEXG).

Patients enrolled in our study had mean age of 62.98±6.664years in PEX group and 65.32±6.628years in PEXG group. L de Juan Marcos et al116, in their study had mean age of 77.2±7.3 years .Mineo Ozaki et al[31], in their study had mean age of 78 years .EleftheriosAnastasopoulos et al[32], in their study had mean age of 73.4 years . The mean age in our study is lower as compared to other studies. However,the majority of cases in our study are above 60 years explaining the late onset of the disease.

In our study, the gender distribution was 72.50% males and 27.50% females .This is comparable to the studies conducted by Min Sagong et al[33] and YetkinYaz et al[34], with malegender being predominant in their studies. There was a statistically significant difference in gender distribution showing a male predilection for the disease.

In the present study, the cases with outdoor and indoor activity were 72.50% and 27.50% respectively. Similar observations were also reported by Ravi Thomas et al[35]. The association of occupation with pseudoexfoliation can be explained by the fact that the people engaged in outdoor activities are more exposed to the environmental factors like solar radiations which may be a risk factor for the disease.

In our study, pseudoexfoliation was present in 353 eyes of 200 cases. Out of 200 cases it was unilateral in 47(23.5%) and bilateral in 153(76.5%). It was present on pupillary margin in 125(35.41%) eyes, on anterior lens capsule in 175(49.58%) eyes and in both locations combined in 53(15.01%) eyes. The results are contrary to that seen by Alan P Rotchfordet al[36], who observed that maximum patients had pseudoexfoliation at pupillary border. However, our observations are in agreement with Ravi Thomas et al[35]. In their study, exfoliative material was present on anterior lens capsule in 42.9%, on pupillary margin in 33.9% and in both locations in 23.2% of eyes.

In our study, predominant cataract was nuclear cataract(49.47). Higher percentage of nuclear cataract was also observed in the study conducted by K Kaljurand et al[37]. In their study nuclear cataract predominated in eyes with pseudoexfoliation(57.6%).Similar observations were also made by J. Hietanen et al[38].

In the present study, majority of the eyes (58%) were blind (distance visual acuity of < 6/60) , followed by visual impairment in 28%. Our results were comparable to the study conducted by Ravi Thomas et al[35]. They found that 43.5% of eyes withpseudoexfoliation were blind and 31.6% of eyes were visually impaired. Similar observations were made by Allan P Rotchfordet al[36].

In the present study, the median CDR in PEX group was 0.2(range 0.1-0.3), in PEXG group it was 0.6(range 0.4-0.8). Glaucomatous atrophy was seen in 40 eyes in PEXG group. These observations were comparable to study conducted by YetkinYaz et al[34]. In their study median CDR in PEX and PEXG group was 0.2 and0.6 respectively. Similar results were obtained by KKaljurand et al[37] and Mineo Ozaki et al[31].

In our study, the mean IOP was 17.26mmHg in PEX group and 24.39mmHg in PEXG group. YetkinYaz et al114, in their study had found similar results with mean IOP in PEXG group 22.25mmHg, and 14mmHg in PEX group. Our results were also comparable to studies conducted by Allan P Rotchfordet al[36] and J. Hietanen et al[38].

Several studies have pointed that cornea is thinner in pseudoexfoliation (Miyake K et al[39], and Ozcura F et al[40]). These alterations are secondary to changes in endothelial cells because corneal thickness is an indirect indicator of endothelial function. The mean central corneal thickness in pseudoexfoliation patients has been reported as 507±25µm(Ventura AC et al[41]), 528±30 µm(Puska P et al[42]) which was comparable to our study (531.80±19.127µm).

Conclusion:-

The prevalence of PEX is found to increase with age. Patients with PXG had more severity of optic nerve damage at presentation. Therefore a careful assessment for detection of PEX is warranted and regular follow-up of patients is desired to minimize the extent of optic nerve damage. Majority of PXF Patients were rural residents. Increased prevalence of PXF was seen in patients exposed to outdoor activity. Pseudoexfoliation syndrome may cause a spectrum of serious ocular and surgical complications. The problems related to cataract surgery are mainly initiated by zonular instability and, to some degree, by insufficient pupillary dilation. Thus awareness of the structural and functional features of this disorder may help avoid or minimize most of them. The early recognition of the syndrome has increased the percentage of favourable outcomes in operative procedures, through careful consideration with preoperative preparation, surgical awareness and postoperative follow-up

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