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First-degree relatives of patients with angle-closure disease: A biometric evaluation

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Abstract

Purpose: This study aims at examining patients across primary angle-closure disease (PACD) spectrum consisting of PAC suspect (PACS), PAC, and PAC glaucoma (PACG), their untreated first-degree relatives and studying their biometric parameters.
Materials and Methods: Sixty newly diagnosed patients of PACD (22 with PACS, 20 with PAC, and 18 with PACG) were enrolled as index cases. One hundred and eighty-two first-degree relatives of these 60 newly diagnosed patients were enrolled as study population of relatives. Biometric parameters of relatives were compared with index cases. Overall incidence and relative risk (RR) of getting angle-closure disease among first-degree relatives were analyzed.
Results: Axial length (AXL), anterior chamber depth (ACD), and aqueous depth (AQD) were highest in index cases of PACS followed by PAC and then PACG. In our study, mean AXL was found to be the shortest in the index cases of PACG (22.18±0.23 mm) as compared to PAC (22.85±0.24 mm) and PACS (22.56±0.15 mm). ACD and AQD followed the disease severity trend, being highest in PACS group followed by PAC and then PACG. In relatives, a significant difference was found in mean AQD of index cases and unaffected relatives ($P \leq 0.001$), AQD being higher in the latter. Nearly a third (31.1%; 19/61) siblings of PAC and PACG together had the angle-closure disease, while 38.46% (10/26) siblings of PACS had the angle-closure disease. The RR of having PAC was much higher in PACG relatives (1.83) than PAC relatives (0.74) as compared to the baseline population of PACS relatives. Thus, the RR of having any subtype of PACD was much more in first-degree relatives of PACG (1.44) than those of PAC (0.82).
Conclusion: Parameters, such as ACD, AQD, and AXL, follow a disease severity trend and can be used for population screening. First-degree relatives, especially siblings of patients with PACG, must undergo screening for timely detection of angle-closure disease.

Introduction

A glaucoma is a group of chronic ocular disease which is characterized by progressive degeneration of retinal ganglion cells and their axons, leading to nerve fiber layer loss, optic disc cupping, and consecutive corresponding visual field changes.[1] Whether manifesting as primary open-angle glaucoma (POAG) or primary angle-closure disease (PACD), glaucoma is known to have a significant genetic basis. The genetic preponderance of PACD is expected. This is because, as compared to POAG, PACD has been found to be dependent on many anatomical factors, predominantly determining the anterior chamber dynamicity. The dynamicity of the anterior chamber is mainly responsible for the angle closure to take place. A positive family history has been cited as one of the important predisposing risk factor for PACD.[2,3] Studies done so far have established heritability of the biometric parameters such as anterior chamber depth (ACD) in PACD patients and their relatives.[4-6] However, most of these studies suggest a familial risk of angle closure, the heritability, and sibling risk of PACD which remains largely

unknown. The present study aims at examining patients across PACD consisting of PAC suspect (PACS), PAC, and PAC glaucoma (PACG), their untreated first-degree relatives and studying their biometric parameters.

Materials and Methods

This prospective and descriptive study was carried out at a tertiary care center of North India. Sixty newly diagnosed patients of angle-closure disease (22 PACS, 20 PAC, and 18 PACG) were enrolled as index cases from Glaucoma Clinic of Department of Ophthalmology, Government Medical College and Hospital, Chandigarh. All possible first-degree relatives of these index cases with age more than 18 years, of either gender and who were untreated, were called up for examination by either writing to them or telephonically calling them, according to the contact information provided by the index cases.

Patients with any previous intraocular surgery, uveitis, or any active inflammation in the eye, history of medical, laser or surgical treatment for glaucoma, significant cataract, or history of use of steroids or drugs that may alter the iris-lens diaphragm configuration were excluded from the study. After getting ethical approval for the study from the institute, an informed consent was taken from index cases as well as relatives before examining them. The study conformed to the tenets of the Declaration of Helsinki.

A detailed history and comprehensive ocular examination, including best-corrected visual acuity, slit-lamp biomicroscopy, calibrated Goldmann applanation tonometry, Zeiss 4 mirror gonioscopy (modified Schaffer's grading), white on white perimetry with Humphrey's visual field analyzer 750II (Humphrey-Zeiss Instruments, Dublin, California, USA) using 24-2 Swedish Interactive Threshold Algorithm Fast Strategy(SITA-FAST), and optic disc evaluation using +90 D lens with slit-lamp biomicroscopy, was done.

Biometric parameters such as axial length (AXL), ACD, aqueous depth (AQD), lens thickness (LT), central corneal thickness (CCT), and pupillary diameter (PD) were noted using non-contact biometry (optical low coherence reflectometry using LENSTAR LS 900® Haag-Streit International, Koeniz, Switzerland). Biometric parameters of the affected eye were only taken for analysis in index cases as well as relatives. The first-degree relatives were classified as affected with the angle-closure disease and unaffected. Affected relatives were further classified as PACS, PAC, and PACG according to the angle-closure disease classification given by the international society of geographical and epidemiological ophthalmology as follows:

PACS: An eye with an anterior chamber angle wherein >180° of the posterior pigmented trabecular meshwork is not seen (occludable angle).

PAC: An eye with an occludable drainage angle and features indicating that trabecular obstruction by the peripheral iris has occurred, such as peripheral anterior synechiae, elevated IOP, iris whorling, "glaucomfleken" lens opacities, or excessive pigment deposition on the trabecular surface. The optic disc does not have evidence of glaucomatous damage in the form of cupping or neuroretinal rim loss.

PACG: PAC together with evidence of glaucomatous optic neuropathy.[7] The incidence of angle-closure disease was calculated in each subgroup of relatives.

The relative risk (RR) of being affected was calculated taking the population of relatives of PACS as a baseline population.

Statistical analysis

Socio-demographic variables such as age and gender, clinical variables such as primary diagnosis (PACS, PAC, and PACG), etc., were taken as explanatory parameters. AXL, AQD, ACD, LT, CCT, and PD were taken as outcome variables. Descriptive analysis of all the explanatory and outcome parameters was done. All the categorical variables were presented in the form of frequencies and percentages. The numerical variables were presented in means and standard deviations. The association between explanatory and outcome parameters was assessed by calculating the mean, mean difference, F-statistic, and their 95% CI and p-value by ANOVA test. IBM SPSS statistical software version 21 was used for statistical analysis. $P < 0.05$ was taken as significant.

Results

Out of the 60 index cases, there were 41 (68.3%) females. The primary diagnosis was PACS in 22 (36.7%) of the participants, PAC in 20 (33.3%), and PACG in 18 (30%) of the participants, making PACS the most common diagnosis. There were total of 182 first-degree relatives which were finally screened biometrically.

Results for affected relatives

Out of the total 75 children in first-degree relatives of probands, 17 (22.66%) were affected (PACS/PAC/PACG) with the angle-closure disease. However, out of 87 siblings, 29 (33.33%) were affected. Twelve out of 20 parents (60%) were affected with the angle-closure disease. Demographic characteristics and biometric parameters of the affected and unaffected relatives in each group were compared with their respective index cases. The results obtained are shown in Table 1.

The incidence of angle-closure disease in all three subgroups of relatives was calculated. A total of 65 relatives of PACS probands were included in the final analysis, out of which 19 (29%) had the angle-closure disease (13 [20%] had PACS and 6 [9%] had PAC), while 46 (71%) were unaffected. None of the relatives had PACG. However, out of 58 relatives of probands with PAC included in the final analysis, 14 (24%) had the angle-closure disease (10 [17%] had PACS, and 4 [7%] had PAC), while 44 (76%) had no abnormality. None of the relatives had PACG. A total of 59 relatives of probands of PACG were included in the final analysis, out of which 25 (43%) had the angle-closure disease, 14(24%) had PACS, 10 (17%) had PAC, and 1 (2%)

Table 1: Biometric parameters of the study population (primary angle-closure glaucoma, primary angle-closure, primary angle-closure suspect, axial length, anterior chamber depth, aqueous depth, lens thickness, central corneal thickness, and pupillary diameter

Parameters	PACS (*n*=22)	Relatives (*n*=65)				PAC (*n*=20)	Relatives (*n*=58)				PACG (*n*=18)	Relatives (*n*=59)			
		PACS (13)	PAC (6)	PACG (0)	Open angles (46)		PACS (10)	PAC (4)	PACG (0)	Open angles (44)		PACS (14)	PAC (10)	PACG (1)	Open angles (34)
Mean AXL (mm)	22.56±0.09	22.68 (*P*=0.61)	22.21 (*P*=0.22)	NA	23.11 (*P*=0.003)	22.85±0.24	22.57 (*P*=0.40)	23.09 (*P*=0.67)	NA	23.16 (*P*=0.18)	22.18±0.22	22.71 (*P*=0.11)	22.25 (*P*=0.84)	23.18 (*P*=0.31)	23.35 (*P*<0.001)
Mean AQD (mm)	2.09±0.04	2.22 (*P*=0.04)	2.09 (*P*=0.93)	NA	2.72 (*P*<0.001)	2.04±0.03	2.14 (*P*=0.01)	2.17 (*P*=0.09)	NA	2.59 (*P*<0.001)	1.93±0.04	2.32 (*P*=0.00)	2.05 (*P*=0.13)	1.97 (*P*=0.84)	2.59 (*P*<0.001)
Mean ACD (mm)	2.60±0.04	2.75 (*P*=0.02)	2.60 (*P*=0.97)	NA	3.24 (*P*<0.001)	2.54±0.04	2.68 (*P*=0.02)	2.73 (*P*=0.05)	NA	3.13 (*P*<0.001)	2.44±0.05	2.88 (*P*=0.00)	2.57 (*P*=0.12)	2.48 (*P*=0.85)	3.12 (*P*<0.001)
Mean LT (mm)	4.48±0.08	4.19 (*P*=0.02)	4.71 (*P*=0.19)	NA	4.11 (*P*<0.001)	4.51±0.09	4.29 (*P*=0.14)	4.07 (*P*=0.44)	NA	4.01 (*P*<0.001)	4.50±0.1	4.23 (*P*=0.05)	4.58 (*P*=0.53)	3.97 (*P*=0.24)	4.02 (*P*<0.001)
Mean CCT (μ)	518±0.04	531.15 (*P*=0.10)	524.00 (*P*=0.55)	NA	522.04 (*P*=0.61)	536±0.07	537.30 (*P*=0.90)	535.75 (*P*=0.99)	NA	528.44 (*P*=0.44)	520.77±0.06	531.79 (*P*=0.15)	522.1 (*P*=0.87)	514.0 (*P*=0.79)	533.3 (*P*=0.12)
Mean PD (mm)	4.15±0.15	4.19 (*P*=0.84)	3.90 (*P*=0.42)	NA	4.52 (*P*=0.03)	3.92±0.15	4.15 (*P*=0.34)	3.91 (*P*=0.96)	NA	4.23 (*P*=0.05)	4.01±0.18	4.17 (*P*=0.52)	4.14 (*P*=0.59)	4.01 (*P*=0.99)	4.32 (*P*=0.08)

PACG: Primary angle-closure glaucoma, PAC: Primary angle closure, PACS: Primary angle-closure suspect, AXL: Axial length, AQD: Aqueous depth, LT: Lens thickness, CCT: Central corneal thickness, PD: Pupillary diameter

had PACG). However, 34 (57%) were unaffected. The least severe form of the angle-closure disease, the PACS group of relatives, was taken as baseline population, and RR of getting the disease was calculated in the remaining two subgroups.

Considering the relatives of PACS proband as a baseline, the RR of having PACS, PAC, or PACG in relatives of the other two groups of probands was calculated [Tables 2 and 3]. None of the relatives in the PACS (baseline) group had PACG; hence, the RR could not be computed. The RR of having PAC was 0.74 times in relatives of PAC and 1.83 times in relatives of PACG, compared to baseline. The RR of developing PACS was 0.86 times in relatives of PAC and 1.18 times in relatives of PACG, compared to baseline. The RR of having any abnormality (PACS/PAC/PACG) was 1.44 times in relatives of PACG and 0.82 times in relatives of PAC, compared to baseline (relatives of PACS).

Discussion

Angle-closure glaucoma has been found to be more common in the East Asian population as compared to the Western population.[8,9] According to various studies done in the South Indian population, the prevalence of ACG was found to range from 1.48 to 4.32%.[10,11] ACG has been found to have a familial predisposition.[2] Sihota *et al*. studied North Indian patients with PACG and the first- and second-degree relatives of PACG were screened for the angle-closure disease. They found 49.2 % of the relatives (first degree and second degree) affected with the angle-closure disease.[12] In our study, out of the 182 first-degree relatives who were screened for angle-closure disease, 58 were finally found to have angle-closure disease. Thus, the incidence of angle-closure disease was 31.86% among them. According to the various previous studies done in India, angle-closure disease was found to be more common in the age group of 40–60 years.[13,14] In the present study, the mean age of probands as well as affected relatives was similar to that found in the previous studies and was in between 45 and 55 years. It was also found that the severe form of disease affected the older population confirming increasing age as one of the risk factors associated with the severity of disease as studied before by Vijaya *et al*.[11]

According to various population-based studies done in India, angle-closure glaucoma has been found to be more common in women.[12-15] Out of the total 60 probands, 68.3% (41/60) were females in our study. Out of the first-degree relatives who were finally found to be affected with the disease, 51.7% (30/58) were females. Thus, our study also had more prevalence of angle closure in females.

Various studies done so far have concluded that the incidence of PACD is directly related to the variability of biometric parameters such as AXL, ACD, and LT. However, the literature is sparse regarding the variability of these parameters in subtypes of angle-closure disease and their first-degree relatives. Angle-closure glaucoma has been found to be common in eyes with shorter AXL according to various studies.[16,17] In

Table 2: Relative risk of developing subtypes of angle-closure disease in relatives of other probands, compared to PACS (primary angle-closure glaucoma, primary angle-closure, primary angle-closure suspect, and relative risk)

Proband	PACG		PAC		PACS		Unaffected		Total
	No.	RR	No.	RR	No.	RR	No.	RR	No.
PACG	1	NA	10	1.83	14	1.18	34	0.81	59
PAC	0	NA	4	0.74	10	0.86	44	1.07	58
PACS (Baseline)	0	NA	6	1	13	1	46	1	65

RR: Relative risk, PACG: Primary angle-closure glaucoma, PAC: Primary angle closure, PACS: Primary angle-closure suspect

Table 3: Relative risk of developing glaucoma in relatives of other probands, compared to PACS (primary angle-closure glaucoma, primary angle-closure, primary angle-closure suspect, and RR)

Proband	Affected		Unaffected		Total
	Number	RR	Number	RR	Number
PACG	25	1.44	34	0.81	59
PAC	14	0.825	44	1.07	58
PACS (Baseline)	19	1	46	1	65
PACS (Baseline)	19	1	46	1	65

PACG: Primary angle-closure glaucoma, PAC: Primary angle closure, PACS: Primary angle-closure suspect, RR: Relative risk

our study, the mean AXL was found to be the shortest in the probands with PACG (22.18±0.23 mm) as compared to PAC (22.85±0.24 mm) and PACS (22.56±0.15 mm). Thus, these values were similar to those which were noted before by George *et al*.[17] Furthermore, the PACG patients had shorter eyes as compared to other subtypes of angle-closure disease, and this finding corroborated with the findings of Sihota *et al*.[12] In each subtype of angle-closure disease, the mean AXL was shorter in probands as compared to their first-degree relatives. This result also matched with the one found in the study done by Sihota *et al*.[12] There was no statistically significant difference found between AXL of probands of PACS, PAC, and PACG and their affected relatives ($P > 0.05$) suggesting a probable genetic basis in the inheritance of this disease as noted by Lowe.[2]

Andhra Pradesh Eye Disease Study (APEDS) found that short ACD is an important risk factor for PACD.[18] In our study, all three groups of probands had a statistically significant difference in the ACD (p=0.02). The mean ACD noted in the PACG group of probands was 2.44±0.05 mm. In the APEDS, the mean ACD in PACG eyes was found to be 2.53±0.04 mm.[18] Sihota *et al*., had also studied ACD in North Indian eyes and found that the mean ACD was 2.56±0.06 mm in the PACG group.[12] Thus, the mean ACD which was found in our study in the PACG eyes was similar to that seen in the previous studies. The ACD was highest in the probands of PACS group (2.60±0.04mm) followed by PAC (2.54±0.03mm) and lowest in the PACG group (2.44±0.05mm). Thus, it would be safe to assume that the biometric trend of ACD followed the disease severity trend. The biometric trend of ACD of relatives was similar to that of probands. This probably suggests the inheritance factor association in the case of family members of angle-closure disease patients, as noted previously by George *et al*.[17]

It has been known for a long that the dynamicity of ACD is mainly due to varying LT. Saxena S and coauthors reported mean LT in the PACG group to be 4.57±0.34 mm.[19] In our study, the mean LT in the group of PACG probands had a similar value (4.50±0.1 mm). However, there was no statistically significant difference in mean LT between three groups of probands as well as relatives. This finding is similar to that reported by Moghimi *et al*.[20] Probably, this is due to the age factor which mainly confounds this parameter. On comparing the mean LT of all three groups of probands with their respective unaffected relatives (those with open angles on gonioscopy), it was found that the probands had significantly thicker lenses ($P < 0.05$). Thus, the ACG patients had thicker lenses as compared to the normal population in the study group, as reported previously by Lowe.[2]

It has been studied by Aghaian and coauthors that PACG patients have thinner corneas.[21] In a study of anatomical and etiological factors in ACG patients by Lowe, it has been found that the CCT of PACG patients is not statistically significantly different than the normal population.[2] In our study, the mean CCT was statistically different in the three groups of probands ($P = 0.05$), but in the case of relatives, there was no statistically significant difference found in mean CCT. Furthermore, there was no significant difference in mean CCT between probands and their affected relatives ($P > 0.05$).

AQD is defined as the distance from the corneal endothelium to the anterior lens surface. It nullifies the effect of CCT while studying the biometric parameters for ACG. To the best of our knowledge, the literature is sparse as regards the role of AQD in ACG patients. In our study, in index cases and their respective relatives, AQD followed the disease severity trend, being highest in PACS group followed by PAC and then PACG. In the study population of relatives, a statistically significant difference was found in mean AQD of probands and unaffected relatives ($P \leq 0.001$). The mean AQD was higher in unaffected relatives than their respective probands with angle-closure disease. Thus, AQD may be used as an adjunct parameter to screen the population for angle-closure disease, especially in those where measurement of CCT is not possible.

Angle-closure disease has a familial prevalence. In the present study, the total number of siblings who were found to be affected finally was 33.33% (29/87). In a recent study done in the South Indian population with angle-closure disease, Kavitha *et al*. found that a total of 36.7% of siblings of PAC or PACG were having angle-closure disease. However, 35% of the PACS siblings were having angle-closure disease.[22] In the present study, 31.1% (19/61) siblings of PAC and PACG together were having angle-closure disease and 38.46% (10/26) siblings of PACS were having angle-closure disease. The results in the study population are thus similar to those found recently by Kavitha *et al*.

In the present study, the RR of having PAC was much higher in PACG relatives (1.83 times) than PAC relatives (0.74 times)

as compared to the baseline population of PACS relatives. It can be inferred that as the disease severity increases, the chance of first-degree relatives getting PAC also increases. Thus, the RR of having any subtype of angle-closure disease was much more in relatives of PACG (1.44 times) than those of PAC (0.82 times). These results are in agreement with those reported by Sihota *et al*.[12] We can conclude that targeted screening of first-degree relatives of PAC and PACG must be carried out. These populations must undergo both ophthalmological and gonioscopic evaluation.

Conclusion

The worldwide estimate of the number of people with PACG has increased from 2010 to 2020. It is estimated that nearly 90% of patients will be from China, India, and South East Asia and that a quarter of all PACG subjects worldwide will be bilaterally blind by 2020.[23] Therefore, targeted screening must be carried out to prevent visual morbidity due to PACD. The results from our study suggest that targeted screening of family members, especially siblings of PAC and PACG, can help in finding out the hidden cases of the PACD from the community and thus reduce the morbidity.

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