An evaluation of the darkroom prone provocative test in family members of primary angle closure glaucoma patients

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Abstract

Purpose To compare ocular biometric parameters with darkroom prone provocative test (DRPPT) in family members of primary angle closure glaucoma (PACG) patients. **Methods** One hundred and forty-nine family members of 46 PACG patients underwent ocular examination included slit lamp biomicroscopy, gonioscopy, fundus examination using +90 D lens, Goldmann applanation tonometry, darkroom prone provocative test, perimetry on Humphrey's field analyzer II and optic disc evaluation using HRT II. Ultrasonic ocular biometry and the DRPPT were then performed. IOP $\geq$ 8 mmHg rise from baseline with iridocorneal touch was considered as a positive test. **Results** Of the 149 family members examined, 55 (36.9%) were found to have PACG. Forty (72.7%) of these had subacute PACG and 15 (27.3%) were found to have chronic PACG. Thirty-nine (70.3%) of the affected members showed a positive DRPPT. Mean anterior chamber depth (ACD) was 2.03 ± 0.3 , 2.3 ± 0.4 , 2.7 ± 0.3 mm ($P = 0.0001$) and mean lens thickness was 4.41 ± 0.39 , 3.99 ± 0.5 , 3.93 ± 0.4 mm ($P = 0.0001$) in DRPPT positives, borderlines and negatives respectively. ROC curve (ACD) plotted showed cutoff value of 2.07 mm (sensitivity 88.57%) for screening. **Conclusion** Anterior chamber is shallowest, lens is thickest and axial length is shortest in affected and DRPPT positive, family members of PACG patients.

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Primary angle closure glaucoma (PACG) is being increasingly recognized as a major cause of visual morbidity, which could theoretically at least, be prevented or halted by early diagnosis and therapy. PACG eyes and those with occludable angles have shorter axial length (AL), shallower anterior chamber depth (ACD) and thicker lens (LT).^{1–5} Certain racial groups are also reported to be at an increased risk of developing PACG.^{6–9} A positive family history of PACG is an additional risk factor, with a 3.5 to six times higher prevalence of occludable angles in first-degree relatives of PACG patients.^{10–14} The inheritance of PACG is believed to be polygenic^{15–17} although AD and AR inheritance patterns are seen in pedigrees with a high prevalence of PACG. Similar anatomical dimensions in patients and their relatives may explain their predisposition to PACG and conversely any dissimilarity may explain why many relatives are not affected.

Various provocative tests have been devised to induce angle closure and a rise of intraocular pressure (IOP), with conflicting results. Comparative evaluations have shown the pharmacological tests to be time consuming, to have a poor specificity for PACG and they can precipitate an attack of angle closure. The darkroom and prone tests are physiological, but used in isolation, they also have a poor specificity. A combination of the two physiological tests, the darkroom prone test, (DRPPT), is physiologic and has been used as a safe provocative test for PACG. However, there has been no detailed studies to evaluate the utility of this test.

The present study was carried out to evaluate DRPPT in families of PACG patients, and to

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correlate the results with biometric parameters in the different subtypes of primary angle closure glaucoma, PAC suspects or unaffected family members.

Materials and methods

Consecutive patients diagnosed as PACG attending a tertiary care centre who met the inclusion criterion were included in the study. All possible first-degree relatives of the index patients were screened for glaucoma. A detailed history and complete examination including best-corrected visual acuity, slit lamp biomicroscopy, fundus examination using +90 D lens, Goldmann applanation tonometry, darkroom prone provocative test, perimetry on Humphrey's field analyzer II, using 30-2 full threshold strategy and optic disc evaluation using HRT II, was performed.

Gonioscopy was performed using a narrowed slit lamp beam, with the least possible illumination, starting temporally and avoiding the pupil using a Goldmann single mirror gonioscope. Dynamic gonioscopy was performed as required. A modified Spaeth's¹⁸ grading system was used.

The DRPPT was then performed. Applanation tonometry was recorded in an illuminated room using Perkin's tonometer MK2 (Clement Clarke International, Edinburg way, Harlow, Essex, CM20 2TT, England) before starting the test. The room was then darkened and patients were asked to sit with their head prone on a table for 1 h. Patients were instructed to keep their eyes open and were repeatedly spoken to, to ensure that they did not sleep. Perkin's applanation tonometry was repeated after the test in the same darkroom, the only source of light being that of the tonometer. Gonioscopy was repeated to determine the angle status. Illumination was constant for all patients examined.

The DRPPT was interpreted as follows:

Positive test ≥ 8 mmHg rise from baseline, with iridocorneal touch.

Borderline 6–7 mmHg rise, with iridocorneal touch/apparent narrowing of angles.

Negative ≤ 5 mmHg rise, with no narrowing or iridocorneal touch.

Biometric parameters were measured ultrasonically on PacScan 300 (Sonomed, Escalon Medical Corporation, USA), by a technician masked to the results of the DRPPT. The parameters assessed were anterior chamber depth (ACD), axial length (AL), lens thickness (LT), and central corneal thickness. Corrected anterior chamber depth (CACD) was calculated by subtracting central corneal thickness from ultrasonically measured ACD.

Family members were divided into those 'affected' that is, those having any subtype of PACG, primary angle

closure suspects (PAC suspects) and those with open angles. All affected members had IOP ≤ 21 mmHg. Affected members were grouped into various subtypes of glaucoma on the basis of the following definitions.

Affected family members

(a) Subacute PACG—gonioscopically documented presence of peripheral anterior synechiae or clumping of pigment in an occludable angle, that is, one with a steep peripheral iris configuration in which less than 180° of the posterior trabecular meshwork was visible, and an angle recess narrowed to less than 20°. Three IOP measurements on different occasions within normal limits, though there may have been a history of a rise of IOP at some point in time. There may or may not have been a history of unilateral headaches, blurring of vision or coloured haloes occurring periodically and resolving spontaneously within half an hour. This is equivalent to the term PAC used in epidemiological studies.

(b) Acute PACG—the occurrence of an acute attack of angle closure glaucoma—a severe unilateral headache, diminution of vision with nausea/vomiting and the presence of a markedly raised IOP in an eye with a shallow anterior chamber, vertically oval pupil, marked corneal oedema and a closed angle. This is equivalent to the term acute PAC used in epidemiological studies.

(c) Chronic PACG—these were eyes, which had a chronically elevated IOP, gonioscopically confirmed peripheral anterior synechiae of more than 180°, and optic nerve head and visual field changes. These patients may or may not have had any prior symptoms. Acute ACG eyes going into the chronic stage were excluded from this group. This is equivalent to the term PACG used in epidemiological studies.

PAC suspects

These family members had occludable angles, more than 180° of trabecular meshwork not visible gonioscopically without manipulation or indentation along with a steep peripheral iris configuration, but no evidence of PAS/pigment clumping, etc.

Unaffected

These were the family members having gonioscopically open angles (angle recess $> 25^\circ$), with no evidence or suspicion/of PACG.

Cases having any other ocular disease, prior laser iridotomy, and prior surgery were excluded from the study.

Statistical analysis

To avoid duplication of data only the right eye of each patient was studied. Statistical analysis was performed

using STATA 8 software. Comparison between the means was carried out using Wilcoxon sign rank test and Barlett's test. *P*-value <0.05 was taken as significant. Spearman's correlation coefficient was calculated and ROC curves were plotted as required. Weighted Kappa statistics were calculated to rule out the coincidental occurrence of factors.

Results

One hundred and forty-nine family members of 46 index patients were examined. Table 1 shows the groups by diagnosis with their demographic data. After screening 149 family members, 55 (36.9%) were found to have PACG, of which 40 (72.7%) were diagnosed as subacute PACG and 15 (27.3%) of the affected family members were found to have chronic PACG. Forty-four patients (29.5%) overall, were diagnosed to be PAC suspects and

50 (33.6%) were diagnosed as unaffected family members. The mean age of index patients was significantly higher than that of PAC suspects (*P* = 0.012) and unaffected family members (*P* = 0.0001). Similarly, affected family members were significantly older than those unaffected by PACG, (*P* = 0.003).

The DRPPT results are shown in Table 2. Baseline IOP in index eyes having PACG was 17.3 ± 3.5 mmHg and 55.6% showed a positive result on DRRPT, while the rest, 44.4% showed a borderline response. None of these eyes gave a negative response. Thirty-nine (70.9%) of family members diagnosed as any subtype of PACG, that is the affected cases, showed a positive response and 10 (18.1%) showed a borderline response, while 14.6% had a negative result. Among the PAC suspects, 58.5% gave a positive or borderline response, while in those with open angles (the unaffected eyes) a negative response was seen in 63.1% of eyes and a borderline response in 36.8% eyes. None of the open angle eyes had a positive DRPPT response. Family members showing a positive test had a mean IOP rise of 8.58 ± 0.99 mmHg, those with a borderline outcome showed a mean rise of 4.19 ± 0.61 mmHg and the negative test cases had a rise of 1.32 ± 1.0 mmHg (*P* = 0.03).

Family members showing a positive DRPPT had a shallower corrected ACD and thicker lens (*P* = 0.015), as compared to those showing a borderline DRPPT. There was also a significant difference in AC depth between eyes having a negative and borderline result on DRPPT (Table 3). The lens was significantly thicker in patients having a positive DRPPT as compared to those eyes with either a borderline or negative response. Axial length

Table 1 Demographic characteristics in different groups of PACG family members

Diagnosis in family members	No. of cases n (%)	Mean Age $\pm$ SD (years)	M:F ratio
Affected	55 (36.9%)	42.7 ($\pm$ 15.9)	1:1.6
PAC suspects	44 (29.5%)	37.7 ($\pm$ 12.5) ^a	1:1.06
Unaffected	50 (33.6%)	32.3 ($\pm$ 11.6) ^{b,c}	1:0.80
Total	149 (100%)	38.6 ($\pm$ 13.7)	1:1.08

^a*P*-value in comparison to index—0.012.

^b*P*-value in comparison to index—0.0001.

^c*P*-value in comparison affected—0.003.

Table 2 DRPPT results in different groups of family members

Diagnosis	Baseline IOP (mmHg)	Raised IOP (mmHg)	IOP rise (mmHg)	Positive DRPPT n (%)	Borderline DRPPT n (%)	Negative DRPPT n (%)
Index	17.3 ($\pm$ 3.5)	24.5 ($\pm$ 4.5)	7.2 ($\pm$ 3.2)	32 (69.5%)	14 (30.4%)	0 (00%)
Affected	15.3 ($\pm$ 3.3)	21.7 ($\pm$ 4.0)	6.14 ($\pm$ 3.0)	39 (70.9%)	10 (18.1%)	06 (10.9%)
PAC suspects	15.5 ($\pm$ 3.0)	19.3 ($\pm$ 3.8)	3.8 ($\pm$ 2.5) ^{a,b}	07 (15.9%)	19 (43.2%)	18 (40.9%)
Unaffected	14.7 ($\pm$ 3.7)	17.5 ($\pm$ 3.7)	2.7 ($\pm$ 2.1) ^{a,b,c}	00 (0.0%)	18 (36.0%)	32 (64.0%)

^a*P*-value <0.05 in relation to index.

^b*P*-value <0.05 in relation to affected family member.

^c*P*-value <0.05 in relation to PAC suspects.

Table 3 Biometric parameters of eyes showing different responses to DRPPT

DRPPT response	Age (years)	ACD (mm)	CACD (mm)	LT (mm)	AL (mm)
Positive <i>n</i> = 78	43.46 $\pm$ 13.51	2.53 ($\pm$ 0.36)	2.03 ($\pm$ 0.36)	4.41 ($\pm$ 0.46)	22.81 ($\pm$ 0.92)
Borderline <i>n</i> = 43	33.28 ^a $\pm$ 14.67	2.85 ^a ($\pm$ 0.35)	2.3 ^a ($\pm$ 0.35)	3.99 ^a ($\pm$ 0.47)	22.94 ($\pm$ 1.29)
Negative <i>n</i> = 24	35.09 ^a $\pm$ 11.07	3.28 ^{a,b} ($\pm$ 0.39)	2.73 ^{a,b} ($\pm$ 0.38)	3.93 ^a ($\pm$ 0.44)	23.34 ($\pm$ 1.55)

^a*P*-value <0.05 in relation to DRPPT positive.

^b*P*-value <0.05 in relation to DRPPT borderline.

Figure 1 ROC curve between DRPPT and corrected ACD in affected family members.

was similar in eyes having a positive and borderline DRPPT ($P=0.987$).

The rise of IOP following DRPPT was correlated with biometric parameters. The correlation with ACD was significant in index ($P=0.002$) and affected family members (0.0001) but not in the other two groups. Corrected ACD was found to be more significant than ACD ($P=0.001$, 0.0001, respectively) and suspects also had significant P -value ($=0.003$). Lens thickness was not significantly related in PAC suspects ($P=0.084$). The axial length correlated significantly in all the four groups ($P=0.0001$).

A ROC curve plotted for corrected ACD was found to be significant. It showed a sensitivity of 88.57% and specificity of 52.50% for a cutoff AC depth of 2.07 mm. The area under the ROC curve was found to be 78.6% indicating that 78.6% of the family members could be diagnosed accurately, (Figure 1). Weighted Kappa statistics was calculated to rule out a coincidental occurrence of the DRPPT response, and was found to show a moderate agreement ($k=0.4113$) with a P -value of 0.0001 (Landis and Koch's 1977).

Discussion

To our knowledge there is no study in literature evaluating the darkroom prone test with biometric data or among family members of patients having primary angle closure glaucoma. This study evaluated all family members with the DRPPT and then subdivided them clinically into those having PACG, the affected family members, those suspected to have PACG and those with wide-open angles (the unaffected cases).

An early diagnosis of PACG is essential, because there is a safe procedure available, that allows us to, at least theoretically prevent ocular morbidity. The eyes

requiring such tests are those suspected of having intermittent attacks of angle closure or resolved acute PACG and symptom free eyes with shallow anterior chambers and narrow angles on gonioscopy. Towards this goal, many provocative tests have been suggested and evaluated over time.

Many pharmacological tests have been proposed and evaluated, but these are not physiological, have very frequent false negatives, they are time consuming and the patient has to wait for reversal of the mydriasis/cycloplegia. Severe damage has been seen to follow phenylephrine provocative tests in about 10% of eyes.⁷

The darkroom test was first described by Grobholm (1910) and Higitt¹⁹ found 78% of his cases of 'congestive glaucoma' positive on darkroom provocation, while Leydhecker²⁰ reported only 11% of congestive glaucoma suspects to be positive. The IOP was recorded with a Schiotz tonometer before and after 1 h in a darkroom, under normal room lighting. Foulds²¹ studied both normal and PACG eyes, and found a positive response in 51.9% of PACG eyes, with many starting above 31 mmHg. Those starting below 19 mmHg had a positive response in 45.5% of eyes. Normal eyes showed a mean IOP rise of 0.97 ± 2.54 mmHg, 36% of normal eyes showed some rise of IOP and 9% a fall. A mean rise of IOP of 11.1 ± 12.1 mmHg was seen in PACG eyes by Foulds, who commented that the rise in IOP is due to a change in aqueous inflow or the volume of blood in the uvea, with closure of the angle in susceptible eyes. Foulds went on to conclude that though a positive result on the dark test was of great value, a negative result did not in any way rule out the existence of angle closure. Tornquist¹⁷ recorded a rise of >8 mmHg in only 5% of eyes having an anterior chamber shallower than 2 mm.

Hyams *et al*²¹ evaluated PAC suspects and found the dark and mydriatic tests to be negative, while the prone test was positive in 48.6%, and a rise of 6–7 mmHg was seen in a further 25.5%. The prone provocative test was positive in 4.3% of normals with a narrower angle while the darkroom test was negative in normals. They concluded that the darkroom test is very often negative in patients who later develop angle closure glaucoma. The prone test allows forward movement of the lens and the iris possibly provoking angle closure.

In the present study, after screening of family members of PACG index patients, we found that 36.9% had a subtype of primary angle closure glaucoma, a prevalence slightly higher than previously reported. Spaeth²² estimated the frequency of occludable angle among first-degree relatives of Caucasian PACG probands at 20%, four to five times higher than for the population at large. However, the prevalence of PACG among first-degree relatives in the Caucasian population is variously given as 1–12%.^{23,24}

The mean age in index patients was significantly higher than that of PAC suspects ($P=0.012$) and the unaffected family members ($P=0.0001$). Unaffected family members were the youngest, suggesting that with time and thickening of the lens, some of these eyes could also show some evidence of PAC. Foulds²¹ in his study of the darkroom test found that 57.7 ± 11 years was the mean age of individuals who tested positive among PACG cases.

This study agrees well with the findings of the other workers^{17,19,24–27} in that the index patients had significantly shallower anterior chambers ($P=0.0001$), a shorter axial length ($P=0.0001$) and thicker lenses ($P=0.0001$) as compared to unaffected family members.

The anterior chamber depth was least in patients showing a positive response to the DRPT, significantly deeper in those with a borderline response and again a significant difference from eyes with a negative response. The lens was significantly thicker in eyes with a positive DRPT, as compared to the borderline and negative DRPT eyes, which were similar. The axial length was not statistically different among the DRPT response groups. Biometric parameters have not been previously studied in provocative tests for PACG.

In all, 70.9% of the affected family members showed a positive DRPPT and 18.1% showed a borderline response. Foulds²¹ found that 50% cases of ACG showed a darkroom rise of >8 mmHg. Higitti¹⁹ found 78% rise in his cases of congestive glaucomas and Leydhecker²⁰ found a rise of only 11%. We did not perform the test in congestive glaucoma, but in family members who had come for a screening evaluation. Hyams¹⁸ was first to describe the prone test and found 70.2% rise in IOP after 1 h of prone position. Foulds²¹ found that the rise in IOP was related to the initial baseline IOP. In the eyes with IOP 26–30 mmHg the rise was seen maximally as the filtration angle was blocked either functionally or organically and the darkroom may block most of the remaining open sector to give a high rise. In our study, we could not find any such relationship.

In this study, family members suspected to be at risk for angle closure showed a 58.1% positive or borderline response to the dark prone test. Hyams *et al*¹⁸ evaluated PAC suspects found the dark and mydriatic tests to be negative, while the prone test was positive in 48.6%, and a rise of 6–7 mmHg was seen in a further 25.5%. The prone provocative test was positive in 4.3% of normals with a narrower angle while the darkroom test was negative in normals. They concluded that the darkroom test is very often negative in patients who later develop angle closure glaucoma.

No individual with an open angle showed a positive darkroom prone test, but 10.9% of cases with PACG showed negative results in our series. Foulds²¹ stated

that in early cases of angle closure glaucoma the result of darkroom test is likely to be negative, so negative result does not rule out the existence of PACG although the positive test has got more value. There was a significant correlation of a positive DRRPT response with lens thickness and anterior chamber depth in the present study, which signifies the proneness to develop PACG as the lens thickens and the anterior chamber shallows.

The limitations of our study was that it was a cross sectional study and did not look at the changes over time. As PACG can be an asymmetric disease, both eyes can behave differently. However, only one eye was included in the present study. Further longitudinal studies are required on this subject.

In conclusion, the anterior chamber depth is shallowest, lens thickest and axial length shortest in those family members of PACG patients, which have a positive DRPPT and these biometric parameters appeared to move towards more normal values in those where the DRPPT is borderline and negative. A positive DRPPT had a good sensitivity, but only 78.6% accuracy in the diagnosis of PACG in the cohort of patients we studied.

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