

## Evaluation of blotchy pigments in the anterior chamber angle as a sign of angle closure

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**Background:** Blotchy pigments in the anterior chamber (AC) angle are considered diagnostic of primary angle closure (PAC). But there are no reports either on the prevalence of blotchy pigments in AC angles or the validity of this sign. **Aims:** To determine the prevalence of blotchy pigments in AC angles and to evaluate their relationship with glaucomatous optic neuropathy (GON) in eyes with occludable angles. **Setting and Design:** Cross-sectional, comparative study. **Materials and Methods:** Gonioscopy was performed in 1001 eyes of 526 subjects (245 eyes of 148 consecutive, occludable angle subjects and 756 eyes of 378 non-consecutive, open angle subjects), above 35 years of age. Quadrant-wise location of blotchy pigments was documented. **Statistical Analysis:** Odds of blotchy pigments in occludable angles against that in open angles were evaluated. Relationship of GON with blotchy pigments in occludable angle eyes was evaluated using a multivariate model. **Results:** Prevalence of blotchy pigments in occludable angles was 28.6% (95% CI, 22.9-34.3) and in open angles was 4.7% (95% CI, 3.2-6.3). Blotchy pigments were more frequently seen in inferior (16%) and superior quadrants (15%) of occludable angles, and inferior quadrant of open angles (4%). Odds of superior quadrant blotchy pigments in occludable angles were 33 times that in open angles. GON was seen in 107 occludable angle eyes. Blotchy pigments were not significantly associated with GON (odds ratio = 0.5;  $P = 0.1$ ). **Conclusions:** Blotchy pigments were seen in 28.6% of occludable angle eyes and 4.7% of open angles eyes. Presence of blotchy pigments in the superior quadrant is more common in occludable angles. Presence of GON in occludable angle eyes was not associated with blotchy pigments.

**Key words:** Angle closure, anterior chamber angle, blotchy pigments, glaucomatous optic neuropathy, peripheral anterior synechiae

Primary angle closure glaucoma (PACG) is an important cause of ocular morbidity and blindness in the South-east Asian countries.<sup>[1,2]</sup> The prevalence of PACG is almost equal to that of primary open angle glaucoma (POAG) and more importantly, the risk of blindness from PACG is estimated to be 2-3 times greater than that from POAG.<sup>[2-5]</sup>

Primary angle closure (PAC) is a pre-PACG stage in angle-closure disease, wherein the characteristic optic nerve changes and the visual field changes of PACG have not yet developed. Diagnosing and treating angle closure eyes in PAC stage with laser iridotomy is reported to be effective in preventing progression to PACG.<sup>[6]</sup> Peripheral anterior synechiae (PAS) and blotchy pigments in the anterior chamber (AC) angle are considered as diagnostic signs of PAC.<sup>[7]</sup> PAS are acquired adhesions between the corneo-scleral coat and the peripheral iris.<sup>[8]</sup> Blotchy pigments are patchy pigment clumps on the trabecular meshwork or the back part of the cornea [Fig. 1], which are considered "impression of iris pigments, a sign of irido-trabecular contact."<sup>[9]</sup> Though the prevalence of PAS and their association with glaucomatous optic neuropathy (GON) has been reported,<sup>[8]</sup> there are no reports either on the

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**Figure 1:** Blotchy pigments on the trabecular meshwork (black arrows) in an occludable angle after indentation

prevalence of blotchy pigments in AC angles or the validity of this sign in PAC.

The purpose of this study was to determine the prevalence of blotchy pigments and PAS in eyes of Indian subjects and to evaluate their relationship with GON in eyes with occludable angles.

## Materials and Methods

This was a cross-sectional study of new patients who attended the glaucoma clinic of a tertiary eye care facility between January 2007 and August 2007. The study protocol

was approved by the institute's ethics committee. The methods applied in the study adhered to the tenets of the declaration of Helsinki for the use of human subjects in biomedical research.

Inclusion criteria were age above 35 years and willingness to undergo gonioscopy. Exclusion criteria were a history of intraocular surgery or laser procedure anytime in the past, trauma to the eye, presence of pseudoexfoliation, neovascularisation of the iris or AC angle, inflammation in AC or any corneal pathology obstructing a good view of the AC angle.

All eligible subjects underwent a comprehensive ocular examination including visual acuity assessment with Snellen's chart, slit-lamp biomicroscopy, tonometry with Goldmann applanation tonometry (Zeiss AT 030 Applanation Tonometer, Carl Zeiss, Jena, Germany), gonioscopy with Sussman's four mirror gonioscope (Volk Optical Inc, Mentor, OH). Dilated fundus examination with indirect ophthalmoscopy and +90 D lens (Volk Optical Inc) was done in all subjects with open angles at the first visit. In all subjects diagnosed as PAC on gonioscopy, laser peripheral iridotomy was done at the first visit and dilated fundus examination was done a week later.

Gonioscopy was performed by three glaucoma consultants and one glaucoma fellow. The glaucoma fellow had 1 year experience working in the glaucoma clinic. The agreement calculated between one glaucoma consultant and the glaucoma fellow for occludability as well as presence of PAS and blotchy pigments on 40 subjects was excellent ( $\kappa > 0.80$ ). Gonioscopy was performed under standard conditions with the patient looking straight in primary gaze. The room illumination was lowered and the smallest convenient slit beam was used, ensuring that the beam did not fall in the pupillary area. Structures visible in the four quadrants were documented. Angles were diagnosed as occludable if the posterior trabecular meshwork was not visible in at least 180° of the total circumference of the angle in primary position. In eyes with occludable angles, the subject was asked to look toward the mirror for "over the hill" view. Subsequently indentation was performed and the angle opening was noted. In addition, the presence of PAS, blotchy pigments and the quadrant in which they were present were documented. PAC was defined in an occludable angle when there was presence of PAS or blotchy pigments in the angle or when the IOP was more than 21 mmHg.<sup>[7]</sup> Eyes with occludable angles without the above signs of PAC were diagnosed as PAC suspect. PAC eyes with evidence of GON (focal or diffuse neuroretinal rim thinning, localized notching or nerve fiber layer defects) and correlating visual field defects were diagnosed as PACG. Eyes unable to perform visual fields due to poor visual acuity were classified based on optic disc examination.<sup>[7]</sup> VF defects were considered glaucomatous if at least 2 of the 3 Anderson's criteria (3 or more non-edged points in a cluster depressed to  $P < 5\%$  and 1 of which depressed to  $P < 1\%$ , Glaucoma Hemifield Test outside normal limits and pattern standard deviation depressed to  $P < 5\%$ ) were fulfilled.<sup>[10]</sup>

### Statistical analysis

Data from all eligible eyes was considered for analysis. Prevalence of blotchy pigments and PAS in occludable and open angles was estimated. Odds of blotchy pigments in occludable angles

were calculated. The relationship between blotchy pigments and GON was evaluated using logistic regression model which also included presence of PAS, highest recorded IOP, age and gender as predictors. Statistical analyses were performed using commercial software (Stata ver. 11.0; StataCorp, College Station, TX).

## Results

Thousand and one eyes of 526 subjects, visiting our glaucoma clinic for the first time, fulfilled the inclusion criteria and underwent gonioscopy. Of these, 245 eyes of 148 subjects had occludable AC angles and 756 eyes of 378 subjects had open angles. Occludable angle subjects were consecutively recruited while open angle subjects were a nonconsecutive series. Characteristic features of the two groups of subjects are shown in Table 1. The occludable angle group were older, hyperopic, had more females, had a higher IOP and had more cataractous changes of the lens compared to the open angle group. Of the 245 occludable angle eye, 50 eyes were diagnosed as PACS, 88 as PAC and 107 as PACG. In the occludable angle group, 51 eyes of 32 subjects (9 PAC and 42 PACG eyes) had an IOP of 22 mmHg or more at presentation and 80 eyes (17 PAC and 63 PACG eyes) were on some antiglaucoma treatment.

### Blotchy pigments and peripheral anterior synechiae in occludable angles

Blotchy pigments were seen in 70 occludable angle (54 PAC and 16 PACG) eyes, a prevalence of 28.6% (95% CI: 22.9-34.3). Fig. 2 shows the distribution of blotchy pigments in different quadrants of the AC angle. Blotchy pigments were more frequently seen in inferior and superior quadrants. PAS were seen in 147 occludable angle (52 PAC and 95 PACG) eyes, a prevalence of 60.0% (95% CI: 53.8-66.2). Fig. 3 shows the distribution of PAS in different quadrants of the AC angle.

### Blotchy pigments and peripheral anterior synechiae in open angle

Blotchy pigments were seen in 36 open angle eyes, a prevalence of 4.7% (95% CI: 3.2-6.3). Fig. 4 shows the distribution of blotchy pigments in different quadrants of the AC angle. Blotchy pigments were more frequently seen in inferior quadrant compared to other quadrants. PAS were not seen in any of the open angle eyes.

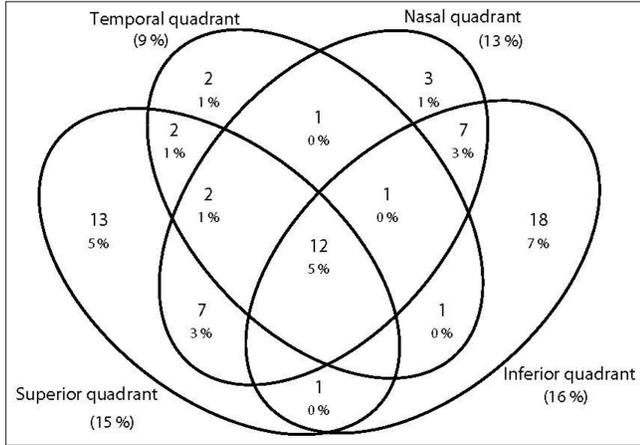
**Table 1: Characteristic features of subjects with open and occludable anterior chamber angles**

	Open angles (756 eyes of 378 subjects)	Occludable angles (245 eyes of 148 subjects)	P-value
Age (years)	51.7 ± 12.0	57.7 ± 11.3	<0.001
Gender (Male:Female)	219:159	65:83	0.004
Spherical equivalent refraction (D)	-0.7 ± 0.1	0.2 ± 0.2	<0.001
Hypertension	79 (20.9%)	47 (31.8%)	0.01
Diabetes	52 (13.8%)	32 (21.8%)	0.03
Intraocular pressure (mm Hg)	14.3 ± 3.3	17.2 ± 7.5	<0.001
Lens (clear:cataract)	400:356	91:154	<0.001

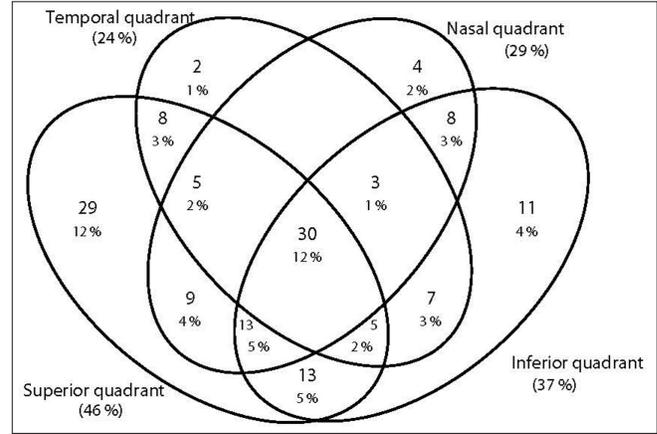
The odds of finding blotchy pigments in occludable angles are shown in Table 2. The odds of finding blotchy pigments in any quadrant of occludable angle were eight times that in open angles. Odds of superior quadrant blotchy pigments in occludable angles were 33 times that in open angles and odds of inferior quadrant blotchy pigments in occludable angles were four times that in open angles.

**Relationship between blotchy pigments and GON in occludable angles**

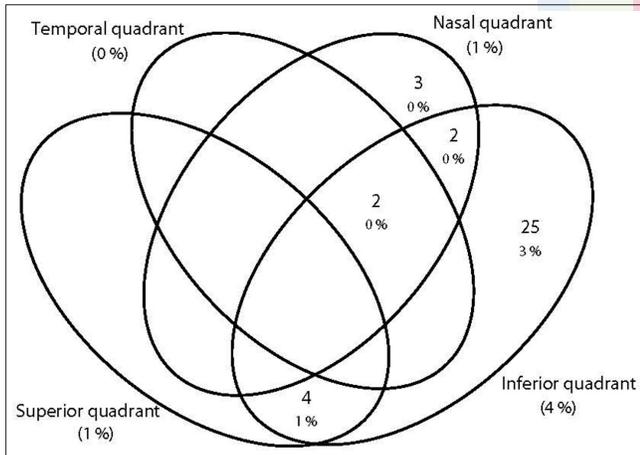
Hundred and seven occludable angle eyes had evidence of GON. Fig. 5 shows the relationship between PAS, high IOP (IOP > 21 mmHg) and blotchy pigments in eyes with GON. PAS were seen in 82% of eyes with GON. Blotchy pigments were seen in 16% of eyes with GON. Blotchy pigments alone without either PAS or high IOP were seen in only 3 eyes (3%) with GON.



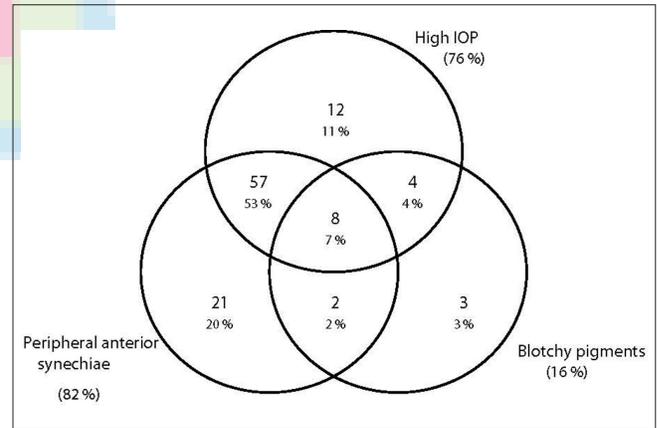
**Figure 2:** Location of blotchy pigments in different quadrants of occludable anterior chamber angle eyes



**Figure 3:** Location of peripheral anterior synechiae in different quadrants of occludable anterior chamber angle eyes



**Figure 4:** Location of blotchy pigments in different quadrants of open anterior chamber angle eyes



**Figure 5:** Presence of blotchy pigments, peripheral anterior synechiae and high intraocular pressure (IOP > 21 mm Hg) in occludable angles with glaucomatous optic neuropathy

**Table 2: Odds ratio (with 95% CI) of blotchy pigments in occludable anterior chamber angles compared to open angles**

	Occludable angle (245 eyes)		Open angle (756 eyes)		Odds ratio
	Blotchy pigments (%)	No blotchy pigments (%)	Blotchy pigments (%)	No blotchy pigments (%)	
In any quadrant	70 (28.6)	175 (71.4)	36 (4.8)	720 (95.2)	8 (5.2 to 12.3)
Inferior quadrant	40 (16.3)	205 (83.7)	33 (4.4)	723 (95.6)	4.3 (2.6 to 6.9)
Superior quadrant	37 (15.1)	208 (84.9)	4 (0.5)	752 (99.5)	33.4 (12.3 to 91)
Nasal quadrant	33 (13.5)	212 (86.5)	7 (0.9)	749 (99.1)	16.7 (7.4 to 37.4)
Temporal quadrant	21 (8.6)	224 (91.4)	2 (0.3)	754 (99.7)	35.3 (9.1 to ∞)

Table 3 shows the results of the logistic regression model evaluating the relationship between GON and the presence of blotchy pigments, PAS and IOP in eyes with occludable AC angles. PAS and IOP were significantly associated with GON while blotchy pigments were not.

## Discussion

In this cross-sectional study, we found that the prevalence of blotchy pigments was 28.6% in occludable angles and 4.7% in open angles. Blotchy pigments in open angles were always found in inferior quadrant except in 4 eyes where in addition to being present in inferior quadrant were also found in superior quadrant and in three other eyes where in addition to inferior quadrant were also found in nasal quadrant. Presence of blotchy pigments in open AC angles was a surprising finding as blotchy pigment, a sign of iridotrabeular contact, would be expected only in eyes with angle closure. The cause of blotchy pigments in open angles is not clear. We had excluded the other possible causes of pigments in the angle like trauma, intraocular surgery, uveitis and pseudoexfoliation. However, possibilities of mild uveitis, missed trauma or some other unknown cause for the blotchy pigments cannot be ruled out. It is also possible that due to more pigmentation in the Indian eye, the AC angle of the eye is predisposed to pigmentation especially in inferior angle as the current of aqueous flows from superior to inferior angle. As all observers were well experienced to detect blotchy pigments, it is unlikely that this increased pigmentation in the inferior angle was misinterpreted as blotchy pigments. The chances of occludable angles being misinterpreted as open angles were also unlikely as the observers were experienced enough to differentiate the two. The relative rarity of blotchy pigmentation in the other quadrants of open AC angles; however, increases the specificity of this sign in diagnosing angle closure.

Evaluating the characteristic features of subjects with open and occludable AC angles, we found that the group with occludable angles was older, hyperopic, had more females, and had more cataractous changes of the lens compared to that with open angles. This is in agreement with the risk factors for angle closure glaucoma reported by various epidemiological studies. Older age, female gender and hyperopia have been shown to be risk factors for angle closure disease in South Indian populations.<sup>[4,5,11,12]</sup> Cataractous lens may be an indication of increasing lens volume, leading to narrowing of the AC angles.<sup>[13]</sup>

**Table 3: Logistic regression model showing the association between glaucomatous optic neuropathy and risk factors in eyes with occludable anterior chamber angles**

Risk factor	Odds ratio	95% CI	P-value
Age	1.02	0.98 to 1.06	0.26
Gender (male as reference)	1.29	0.61 to 2.74	0.51
Highest recorded IOP	1.09	1.03 to 1.16	0.004
Peripheral anterior synechiae	4.09	2.18 to 7.66	<0.001
Blotchy pigments	0.50	0.22 to 1.11	0.10

CI: Confidence interval, IOP: Intraocular pressure

In eyes with occludable angles, blotchy pigments were more commonly seen in the inferior and superior quadrants. However, the odds of blotchy pigments in occludable angles as compared to open angles were the highest for the superior and temporal quadrants. This means that the odds of an eye having angle closure are high if it has blotchy pigments in the superior quadrant. This sign is likely to be of particular help in eyes with doubtful occludable angles.

PAS were seen in 60% of the eyes with occludable angles and the synechiae were more common in the superior quadrant. This is in agreement with the previous studies which have reported that the superior angle is the one to be affected first in PAC and PACG.<sup>[14-15]</sup> None of the open angle eyes had PAS. Foster *et al.* noticed PAS in 0.3- 1.6% of open angle eyes; but as the authors themselves suspected, PAS could have occurred as a consequence of conditions other than primary angle closure, like inflammation, trauma or surgery.<sup>[8]</sup> We had taken care to exclude these conditions in our study.

When we evaluated the relationship of GON with blotchy pigments, PAS and IOP, we found that 82% of eyes with GON had PAS, 76% had IOP > 21 mmHg and only 16% had blotchy pigments. When we evaluated this relationship in a multivariate model, we found similar results, with PAS and IOP being significantly associated with GON and blotchy pigments being insignificant. When we looked at occludable angle eyes without GON ( $n = 138$ ), 43% of these eyes had blotchy pigments, 38% had PAS and 23% had IOP > 21 mmHg. These findings may suggest the natural course of angle closure disease. PACS eyes presumably have intermittent angle closure with iridotrabeular contact leading to blotchy pigments in the occludable angle first, followed by PAS formation at the blotchy pigment location and then by chronic increase in IOP. We however found 3 occludable angle eyes with GON, which showed only blotchy pigments without either PAS or increase in IOP during the examination visit. There is a possibility that the intermittent angle closures which cause blotchy pigments can also cause intermittent spikes in IOP leading to GON. There is also however a possibility that these eyes were normal tension glaucoma eyes developing angle closure now. A longitudinal study of occludable angle eyes with blotchy pigments is required to conclusively determine the natural course of angle closure disease.

Caution should be exercised while interpreting the results of our study. Our study is a hospital-based study conducted at a tertiary eye care facility and does not represent the actual situation in the community. For example, looking at the clinical diagnosis of all occludable angle eyes in our study, the number of eyes with a diagnosis of PACG ( $n = 107$ ) were higher than that of PAC ( $n = 88$ ) and PAC suspect ( $n = 50$ ). Population-based studies conducted in India have unequivocally shown that the prevalence of PAC suspects is much higher than PAC and PACG.<sup>[11,12,16]</sup>

Our study has a few limitations. First, four observers performed gonioscopy examinations of the subjects; of whom three were glaucoma consultants and one was a fellow. However, agreement was formally evaluated only between one of the glaucoma consultants and the fellow, and this was found to be excellent. The other two observers were glaucoma consultants with good experience in gonioscopy and the agreement between them was presumed to be good

but was not formally evaluated. However, gonioscopy is a subjective test. One of the reasons for different estimates of PAC prevalence in different population-based studies done in similar geographic locations in Southern India may be because of the subjective nature of gonioscopy.<sup>[4-5]</sup> Second, though subjects with occludable angles were consecutively enrolled, the subjects with open AC angles were a nonconsecutive series. This might have biased the estimates of prevalence of blotchy pigments as well as the odds ratios. However, the effect of this is unlikely to be significant as the sample size of open angle subjects was large.

In conclusion, blotchy pigments were seen in 28.6% of eyes with occludable AC angles and 4.7% of eyes with open angles. Presence of blotchy pigments in the superior quadrant is more common in occludable angles. Presence of GON in occludable AC angle eyes was significantly associated with the presence of PAS and high IOP but not with blotchy pigments.

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