

Entropion uveae: Early sphincter atrophy, signposting primary angle closure glaucoma?

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PURPOSE. *An easily recognized clinical marker for early changes of primary angle closure glaucoma (PACG) or eyes predisposed to angle closure is important so that timely laser iridotomy can prevent morbidity. Pupillary ruff changes, specifically appearance of entropion uveae (EU), are frequent in eyes with PACG.*

METHODS. *Pupillary ruff was examined under magnification and EU, if present, was graded and correlated with gonioscopic grading and presence of peripheral anterior synechiae (PAS) in consecutive patients with primary open angle glaucoma (POAG), non-glaucomatous controls, and PACG of the subacute, acute, chronic symptomatic, and creeping angle closure glaucoma subgroups.*

RESULTS. *No POAG eye had an abnormal pupillary ruff. A total of 86.7% of subacute PACG eyes and all eyes with acute and chronic PACG showed some grade of EU. Iridocorneal synechiae were more significantly correlated with EU than goniosynechiae ($p < 0.001$). Meridian of iridocorneal but not iridotrabeular synechiae could be correlated with the meridian of EU. In age-matched patients EU was only present in eyes with steep iris configuration, with significant correlation with narrow angles and goniosynechiae. In the detection of PACG the presence of EU Grade I was 94.9% sensitive and 98.2% specific for PACG eyes compared to the gonioscopic picture of angle closure in occludable angles. Its positive predictive value was 91.4%.*

CONCLUSIONS. *EU shows significant correlation with narrow angles, steep iris configuration, and PAS. Kinking of radial iris arteries during angle closure probably causes temporary ischemia, especially of end arteries supplying area of the pupil and sphincter pupillae. EU emerges as an easily observed, objective marker for PACG. (Eur J Ophthalmol 2004; 14: 290-7)*

KEY WORDS. *Pupillary ruff, Primary angle closure glaucoma, Entropion uveae*

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INTRODUCTION

Primary angle closure glaucoma (PACG) constitutes a large percentage of glaucoma cases worldwide, especially in Asia (1). Change in the awareness about PACG has come about because it is now apparent that primary angle closure is not always symptomatic,

and also because of an increased emphasis on gonioscopy in routine ophthalmic evaluation. PACG is unique in that theoretically a prophylactic iridotomy could be enough to prevent the occurrence of angle closure and therefore any glaucomatous morbidity.

There is therefore an urgent need to identify a clinical marker for eyes at risk for PACG, or at least a sign

that occurs in the very early stages of the disease process. A long-term follow-up of angle closure glaucoma suspects was carried out by Wilensky et al (2) that found biometry, gonioscopy, or provocative tests to have no significant predictive accuracy in detecting eyes that would later develop PACG. An anatomic predisposition for PACG has been shown with biometry. However, there is an overlap of the values of these parameters with those of a significant percentage of normal eyes and it is difficult to rely on these to determine eyes requiring an iridotomy. Gonioscopically it is possible to identify some of the eyes at risk of PACG, but even experienced glaucoma specialists may only be able to label an eye as occludable. To the average ophthalmologist the interpretation of gonioscopy in a narrow angle is not easy, more so in the early stages without other clinical features of PACG. There are also many other unknown factors, possibly physiologic, which determine the onset of PACG in anatomically predisposed eyes. An easily recognized clinical marker for early PACG is therefore imperative.

On studying eyes with PACG, we frequently saw a distorted pupillary ruff, the dark pigmented epithelium of the iris that is drawn anteriorly because of the contraction of the sphincter pupillae. The regular width of the ruff was lost, and often it was not visible at all. This was due to the posterior unfolding of the pigment epithelium, giving the appearance of entropion uveae, as opposed to an ectropion uveae where the width of the ruff is increased because of a contraction of the anterior layers of the iris as in late neovascular glaucoma. This entropion uveae was seen even when there were neither symptoms nor other ocular features suggestive of PACG (3, 4). Therefore we prospectively studied the pupillary ruff and correlated it with the gonioscopic picture seen on a Posner four-mirror gonioscope, with the latter being recorded using Spaeth's grading (5). This was carried out in control eyes without any intraocular disease, in eyes with primary open angle glaucoma (POAG), and in eyes with PACG of the subacute, acute, chronic symptomatic, and chronic asymptomatic subgroups.

Methodology

The hospital ethics committee had cleared the study prior to the onset and therefore it has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Cases

Five groups, each comprising 30 consecutive patients diagnosed at the Glaucoma Service with POAG or subacute, acute, chronic symptomatic, or chronic asymptomatic PACG, were studied after informed consent was obtained.

After controlling any initially high intraocular pressure (IOP) medically, pilocarpine was stopped for 2 weeks prior to the study and all measurements were taken when the IOP was less than 20 mmHg

Subacute PACG. A possible history of unilateral headaches, blurring of vision, or colored haloes occurring periodically and resolving spontaneously within half an hour. Gonioscopically documented presence of peripheral anterior synechiae or clumped pigmentation in an occludable angle.

Acute PACG. Recorded occurrence of a congestive episode, a severe unilateral headache, diminution of vision with or without nausea/vomiting, and the presence of a markedly raised IOP in an eye with a shallow anterior chamber, vertically oval pupil, marked corneal edema, and a closed angle.

Symptomatic chronic PACG. These eyes had a chronically elevated IOP of more than 21 mmHg on at least three occasions, gonioscopically confirmed peripheral anterior synechiae, and optic nerve head and/or visual field changes. These patients had a history of unilateral headaches, blurring of vision, or colored haloes occurring periodically. Acute ACG eyes going into the chronic stage were excluded from this group.

Creeping or asymptomatic PACG. These eyes had a chronically elevated IOP of more than 21 mmHg on at least three occasions, gonioscopically confirmed peripheral anterior synechiae, and optic nerve head and/or visual field changes. These patients had no prior symptoms suggestive of angle closure.

POAG. The diagnosis of POAG was made on the basis of at least three records of a raised IOP > 21 mmHg on Goldmann applanation tonometry, open angles on gonioscopy, and disc and or field changes suggestive of glaucoma.

Age refraction and sex-matched control population

One hundred consecutive subjects between 40 and 70 years of age who attended the general ophthalmology clinic underwent a slit lamp and gonioscopic evaluation. The inclusion criteria were a best-corrected visual acuity of at least 20/25 and clear ocular media.

All subacute, chronic PACG eyes, POAG, and patient population eyes had a pupillary diameter of 2.5 to 3.0 mm. In acute PACG eyes the pupillary diameter was not taken as an exclusion criterion as 11 eyes had a diameter of more than 3.0 mm.

Patients were excluded if there was a history of possible ocular trauma, uveitis, or retinal pathology that could affect the iris, or any prior laser therapy or surgical procedure.

A single observer masked to the IOP and gonioscopy of the patients examined the affected eye or, if bilateral, the right eye of each patient. The appearance of the pupillary ruff using a constant magnification on a slit-lamp was noted, looking especially for its width and uniformity. For the ruff to be graded as abnormal, at least two consecutive clock hours had to be involved.

Entropion uveae was graded as follows:

Grade 0—Normal, pupillary ruff raised above the iris plane and of a uniform width of 360 degrees.

Grade I—Pupillary ruff in the plane of the iris but having an uneven width, being less than half of the widest width in that eye, for at least two clock hours.

Grade II—Pupillary ruff completely absent for at least two clock hours.

Gonioscopy was performed in each eye by an observer masked to the diagnosis of the case, using a Posner four-mirror gonioscope, and the results were recorded using Spaeth's grading (4). An eye was diagnosed with PACG if the angle recess was less than 20 degrees and peripheral anterior synechiae could be documented. Peripheral anterior synechiae were recorded as iridotrabecular and iridocorneal synechiae, depending on the point of iris apposition at the angle.

Statistical analysis was carried out using STATA intercooled version 6.0 (Stata Corporation, College Station, Houston, TX). For the diagnosis of PACG, the presence of entropion uveae as a marker was com-

pared to our present gold standard, an occludable angle with peripheral anterior synechiae or clumps of pigment, especially in the superior quadrant. The sensitivity, specificity, rate of false positives and negatives, and positive and negative predictive values were determined. The positive predictive value was calculated by the following formula (6):

$$P(D/T) = \frac{P(D_1)P(T^+/D_1)}{P(D_1)P(T^+/D_1) + P(D_2)P(T^+/D_2)}$$

Where $P(D1/T+)$ = positive predictive value

D_1 = presence of disease

D_2 = absence of disease

T^+ = positive test result

$P(D_1)$ = prevalence.

RESULTS

POAG eyes

The mean age of the POAG patients was 56.1 ± 8.2 years. There were 17 females and 13 males. None of the POAG eyes had an abnormal pupillary ruff. On gonioscopy all POAG eyes had an open angle of at least 30 degrees with an iris insertion into the ciliary body in 21(70%) eyes and at the scleral spur in 9 eyes (30%).

PACG eyes

The mean age of the PACG patients was 55.3 ± 7.9 years: there were 68 females and 52 males. Diabetes mellitus was present in 27 patients and hypertension in 10. On gonioscopy the iris was inserted into the ciliary body in 61 eyes, scleral spur in 47, and indeterminate in 12 eyes because of extensive synechiae and pigmentation.

Subacute PACG eyes

Entropion uveae of some degree, and often of more than one grade, was seen in 26 out of 30 (86.67%) eyes with subacute PACG (Fig. 1). There was an absence of the pupillary ruff, i.e., entropion uveae, Grade II in 7 (23.3%) eyes with subacute PACG. One eye had sectoral iris atrophy associated with Grade II entropion uveae in the same meridian. Iridocorneal synechiae ex-

tending anterior to the Schwalbe's line were seen in nine eyes, of which seven eyes had entropion uveae of Grade II and two eyes had Grade I, corresponding to the meridian of the synechiae. Nineteen eyes had iridotrabecular synechiae of which 17 corresponded to the meridian of the Grade I entropion uveae.

Acute PACG eyes

In the 30 acute PACG eyes, all patients showed the presence of entropion uveae of Grade I and II. In one eye there was sectoral iris atrophy in the superotemporal quadrant. Twenty-two eyes (73.3%) had a total absence of the pupillary ruff, i.e., Grade II entropion uveae, in the direction of the obliquity of the pupil.

Symptomatic chronic PACG eyes

In symptomatic chronic PACG eyes, Grade I was seen in all eyes and Grade II in 19 (63.3%) eyes (Fig. 2). On gonioscopy, symptomatic eyes were found to have iridocorneal synechiae in 27 (90%) eyes. The entropion uveae could be significantly correlated with the site of the iridocorneal synechiae ($p < 0.001$). Iridotrabecular synechiae, i.e., those within the area of the trabecular meshwork, were also seen in 18 (60%) of these eyes. The iridotrabecular synechiae were not correlatable with the meridian of ruff changes ($p = 0.34$).

Creeping or asymptomatic chronic PACG eyes

In asymptomatic chronic PACG eyes or those with creeping chronic PACG, the ruff was not as severely affected. Entropion uveae of Grade 1 was seen in 28 (93.3%) eyes and Grade II in only 3 (10%) eyes. Gonioscopy in asymptomatic chronic PACG eyes showed iridotrabecular synechiae in 25 (83.3%) eyes. Iridocorneal synechiae were seen in 7 (23.3%) eyes. The meridian of pupillary ruff changes was seen to correspond to that of the iridocorneal synechiae in 6 of the 7 eyes but in only 8 of 15 eyes having goniosynechiae alone.

Control eyes

One hundred age-, refraction-, and sex-matched subjects were examined; there were 44 males and 56 females, with a mean age of 55.57 ± 9.8 years. Thirty-three patients were aged 40 to 49 years, 25 were 50

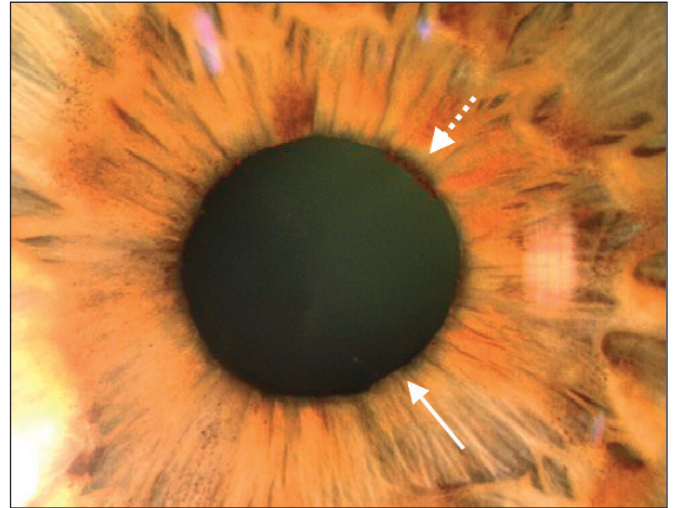


Fig. 1 - Varying width of the pupillary ruff in an eye with subacute PACG. "Entropion uveae" grade I is marked by the dashed arrow and "entropion uveae" grade II by the narrow complete arrow. There is a smoothing of the iris crenations superiorly.

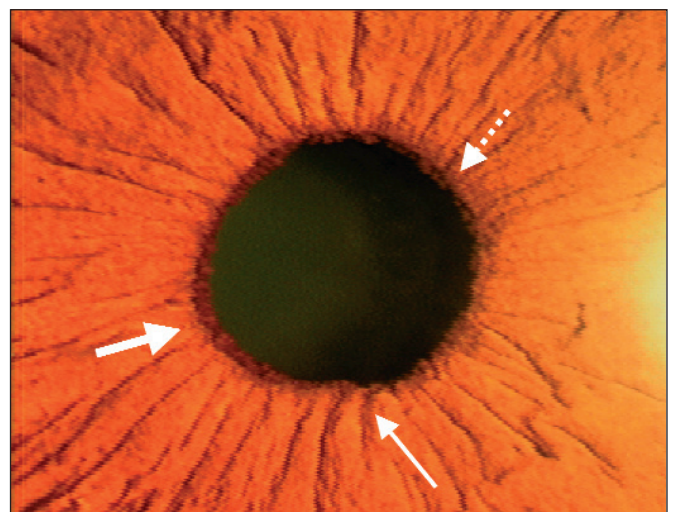


Fig. 2 - Pupil of an eye having symptomatic chronic PACG. There are small areas of normal ruff or "entropion uveae" grade 0 (broad arrow), and "entropion uveae" grade I (dashed arrow). There is an extensive area showing an absence of the pupillary ruff, "entropion uveae" grade II (narrow arrow).

to 59 years, and 42 were 60 to 69 years of age. Twenty-two individuals were diabetics and five patients had systemic hypertension. On gonioscopy in this patient population, the angle width ranged from 10 to 45 degrees. The configuration of the peripheral iris was steep in 82 eyes, regular in 16, and queer or concave in 2.

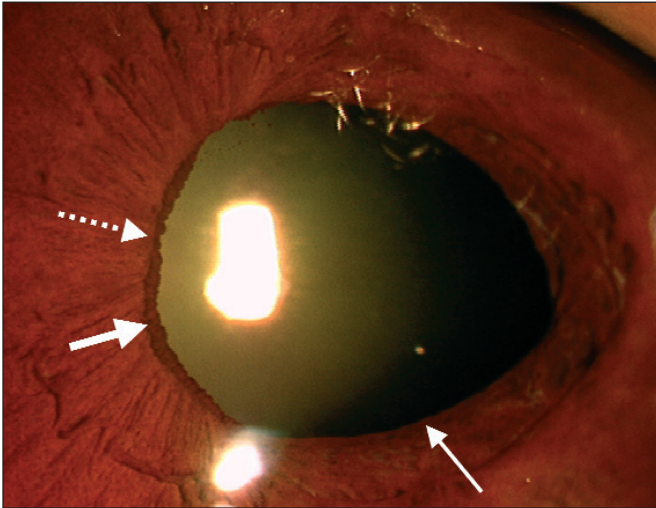


Fig. 3 - Pupil of an eye with resolved acute PACG. Extensive "entropion uveae" Grade II (narrow arrow) is seen to the right, with an isolated area of "entropion uveae" grade I (dashed arrow). Iris features are lost inferiorly and smoothed out superiorly. A normal pupillary ruff can be seen only at about 8.00 o'clock (broad arrow).

The iris was inserted into the ciliary body in 67 eyes, the scleral spur in 30, and the posterior trabecular meshwork in 3 eyes. There were iridotrabecular synechiae present in 18 eyes.

The pupillary ruff in 81 eyes of the patient population studied showed a uniform ruff (Fig. 3), being marginally wider superiorly than inferiorly. All these eyes had a ruff that was elevated with respect to the surrounding iris. The pupillary ruff was abnormal, having Grade I entropion uveae in at least one quadrant in 19 eyes. However, in two of these eyes there was an occludable angle without evidence of closure. Grade I entropion uveae was present only in eyes with a steep peripheral iris configuration. Correlation with the point of iris insertion showed that 15% of eyes with an iris inserted into the anterior surface of the ciliary body, 29.9% with a scleral spur insertion, and one of two eyes with a trabecular meshwork insertion had accompanying entropion uveae.

An analysis of variance found that the entropion uveae significantly correlated with angle width ($p=0.042$), but not with age. Using Spearman correlation coefficient, pupillary ruff atrophy and the presence of goniosynechiae were significantly related ($p<0.001$). The iris insertion could also be significantly correlated with entropion uveae ($p=0.009$).

There was a flattening of the pupillary contour in four of the eyes with entropion uveae.

The involvement of the pupillary ruff in four quadrants of the eyes studied is detailed in Table I.

In primary open angle eyes there was no evidence of closure on gonioscopy and none of the eyes showed the presence of entropion uveae. In both the acute and chronic symptomatic PACG groups both the tests were positive in all eyes, with entropion uveae of both Grade I and II being seen in all eyes. Subacute PACG eyes had a Grade I entropion uveae in 26 eyes, but Grade II only in 16 eyes. Creeping angle closure eyes had Grade I entropion uveae in 28 eyes. In an age- and sex-matched population, 18 eyes had an occludable angle and evidence of closure on gonioscopy, while Grade I entropion uveae was seen in 17 of these eyes and two others with an occludable angle, but without evidence of closure. All eyes with Grade II entropion uveae also had Grade I present in some area of the ruff (Tab. II).

A comparative analysis of gonioscopic positivity for angle closure glaucoma and the presence of Grade I entropion uveae was conducted. Entropion uveae Grade I was found to be 94.9% sensitive for the detection of PACG eyes, and 98.2% specific. The false positive rate for Grade I entropion uveae alone was 1.8% and the false negative, 5.1% (Tab. III). The prevalence of gonioscopically proven PACG in an age- and sex-matched ophthalmic patient population was 18%. The positive predictive value was 91.4%, i.e., of every 100 patients tested positive for entropion uveae, 91.4 would require therapy.

Picking up the subtle changes of entropion uveae Grade I may not always be easy, but the more obvious entropion uveae Grade II was not as commonly seen in subacute eyes, where the diagnosis of PACG is most important. Its sensitivity was 46.4%, specificity 100%, false positive rate 0%, and false negative rate 53.6%.

DISCUSSION

Early identification of eyes at risk of PACG would allow ophthalmologists to perform an early iridotomy and theoretically prevent or halt the progression of peripheral anterior synechiae. Iridotomy is a relatively safe procedure and in races where only a few individuals are likely to develop PACG, one could con-

TABLE I - DISTRIBUTION OF ENTROPION UVEAE IN EYES WITH DIFFERENT SUBTYPES OF PRIMARY ANGLE CLOSURE GLAUCOMA AND IN CONTROLS

Group	Entropion uveae	Eyes affected	Superotemporal	Superonasal	Inferotemporal	Inferonasal
Control population (100 eyes)	Grade I	17	5	2	16	5
	Grade II	0	0	0	0	0
POAG (30 eyes)	Grade I	0	0	0	0	0
	Grade II	0	0	0	0	0
Subacute PACG (30 eyes)	Grade I	26	14	19	23	16
	Grade II	7	1	3	3	1
Acute PACG (30 eyes)	Grade I	30	18	14	22	18
	Grade II	30	22	26	17	15
Chronic symptomatic PACG (30 eyes)	Grade I	23	10	17	20	12
	Grade II	19	5	10	12	8
Chronic asymptomatic PACG (30 eyes)	Grade I	28	12	22	25	13
	Grade II	8	0	1	2	0

POAG = Primary open angle glaucoma; PACG = Primary angle closure glaucoma

TABLE II - DIAGNOSTIC COMPARISON OF GONIOSCOPY WITH THE DETECTION OF ENTROPION UVEAE IN THE DIFFERENT SUBTYPES OF PRIMARY ANGLE CLOSURE GLAUCOMA AND A MATCHED PATIENT POPULATION

Diagnosis	Gonioscopic closure positive	Entropion uveae positive	Gonioscopic closure negative	Entropion uveae negative	Total eyes
Open angle glaucoma	0	0	30	30	30
Subacute PACG	30	26	0	4	30
Acute PACG	30	30	0	0	30
Chronic symptomatic PACG	30	30	0	0	30
Chronic asymptomatic PACG	30	28	0	2	30
Control population	18	17 + 2*	82	81	100

* Two eyes with an occludable angle but no evidence of angle closure.

PACG = Primary angle closure glaucoma

TABLE III - TWO-BY-TWO TABLE FOR CALCULATING THE SENSITIVITY AND SPECIFICITY OF THE PRESENCE OF ENTROPION UVEAE IN THE DETECTION OF PRIMARY ANGLE CLOSURE GLAUCOMA IN GONIOSCOPICALLY CONFIRMED CASES AND NONCASES OF PRIMARY ANGLE CLOSURE GLAUCOMA

	Entropion uveae positive	Entropion uveae negative
Cases (138)	131	7
Noncases (112)	2	110

ceivably do an iridotomy for all eyes with an occludable angle. In Asians, PACG is seen as often if not more often than open angle glaucoma and so there appears to be an anatomic predisposition to narrow angles. In such races it is even more difficult to distinguish between eyes predisposed to PACG and normal eyes.

Iris changes such as sector or sphincter atrophy are described in acute PACG and have been ascribed to ischemia. Such changes are not a regular feature of intermittent or subacute eyes, however, in which an iridotomy would prevent progression to an acute or

chronic form of PACG.

On examination of eyes with PACG we commonly found alterations in the pupillary ruff and therefore undertook this controlled, prospective study of the pupillary margin. None of the eyes with POAG had any pupillary ruff changes. Among the control population studied, entropion uveae was present only in eyes with a narrow angle, and could be statistically correlated with the presence of iridotrabecular synechiae. In our study, entropion uveae was found to be significantly correlated with narrow anterior chamber angles and the presence of peripheral anterior synechiae, the hallmarks of PACG. A raised IOP alone does not cause it, as POAG eyes with comparable IOP showed no pupillary ruff changes. Absence of the pupillary ruff, or a Grade II entropion uveae, is readily detectable, but is not present in early PACG.

The pupillary ruff is formed by the anterior termination of the pigment layer lining the posterior surface of the iris, which is drawn forward by its close association with the contracting sphincter muscle. This leads to the appearance of crenations, mamelons of Gallemaerts, or a physiologic ectropion of the iris. The ruff has been measured to be about 0.06 mm and 0.03 mm, respectively, in the upper and lower half and to have a smooth contour and regular width in normal eyes (7). The blood supply to the iris is from the major arterial circle near the iris root. The arteries enter the iris in several layers at an acute angle and then branch in a dendritic manner, before forming an incomplete anastomosis at the minor arterial circle at the collarette. Branches from the minor circle pass directly to the pupillary margin and also extend posteriorly between the sphincter muscle bundles to supply it and the posterior iris (8).

The pathomechanism of PACG is thought to be a relatively increased pressure in the posterior chamber as compared to the anterior chamber of the eye that bows the iris forward. This angulation of the iris at its root and its compression against the cornea could kink or compress the iris vessels leading to a temporary ischemia and possibly endothelial damage with resultant tissue necrosis. The presence of an incomplete anastomosis at the collarette and end arterial branches to the pupillary margin and sphincter would appear to put the pupillary margin at greatest risk. This has been corroborated by our findings of isolated entropion uveae or one associated with sectoral

iris changes in predisposed eyes and those affected by PACG. The occurrence of pupillary ischemia would depend on whether peripheral anterior synechiae involved a radial artery and also on the degree of anastomosis at the minor arterial circle. This could explain the fact that not all peripheral anterior synechiae resulted in entropion uveae. Fluorescein angiography in pigmented eyes does not allow the documentation of minor vascular changes.

In the presence of generalized iris atrophy as in chronic uveitis, the pupillary ruff can also be abnormal. Further work is required to elucidate the pupillary ruff changes in uveitis, trauma, and other diseases such as diabetic neuropathy.

The reflection of the illuminating bulb in the photo slitlamp makes it difficult to photograph the pupil, and the presence of the iris shadow makes the comparison of the ruff difficult in photographs of the pupil especially in pigmented eyes. The pupillary ruff and its changes can be easily observed with the magnification of the slit lamp.

Foster et al (9) have described a method of assessing the peripheral anterior chamber depth to detect eyes at risk of PACG. The 15% grade of peripheral anterior chamber depth (equivalent to the traditional Grade I) is often difficult to appreciate and yielded sensitivity and specificity of 84% and 86% respectively for the detection of occludable angles. The 5% grade gave sensitivity of 91% and specificity of 93% for the detection of PACG. The subjectivity in assessing entropion uveae seems less as it is readily perceivable as an uneven width of the pupillary ruff over 360 degrees, or its absence. Peripheral AC depth is a measure of an occludable angle, which may or may not go into angle closure. Entropion uveae identifies occludable angles with early evidence of closure.

The presence of entropion uveae should alert an ophthalmologist to the necessity for gonioscopy and the possibility of PACG. As compared to the present gold standard of gonioscopy, its sensitivity and specificity were high and its positive predictive value was 91.4%, i.e., of every 100 patients tested positive for entropion uveae, 91.4 would require therapy. Simply observing the pupillary ruff under magnification would pave the way for an earlier diagnosis and treatment of the early stages of PACG.

Entropion uveae appears to be a reliable marker for PACG, before optic nerve damage begins, and is more

readily recognized and quantifiable than peripheral anterior chamber depth comparisons or gonioscopy. This is a promising aid in identifying eyes at risk of visual loss from PACG.

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