Confirmation of the Presence of Uveal Effusion in Asian Eyes With Primary Angle Closure Glaucoma

An Ultrasound Biomicroscopy Study

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Objective: To confirm the presence of uveal effusion in the eyes of Asian patients with primary angle closure glaucoma (PACG) using ultrasound biomicroscopy (UBM).

Methods: In this observational case series, 70 patients with PACG (28 untreated patients with newly diagnosed PACG and 42 patients who had undergone previous laser iridotomy and were being monitored) and 12 patients with acute primary angle closure (APAC) were recruited. Eyes of patients with newly diagnosed PACG and APAC underwent UBM before and after laser iridotomy, whereas eyes of patients with treated PACG underwent UBM at enrollment. Uveal effusion was defined as a clear space between the choroid and sclera and was graded as follows: grade 0, none; grade 1, slitlike; grade 2, bandlike; and grade 3, obvious.

Results: Overall, uveal effusion was found in 11 of 70 eyes with PACG (15.7%; 95% confidence interval, 8.8%-26.2%) and in 3 of 12 eyes with APAC (25%; 95% confidence interval, 8.0%-53.4%). For patients with newly diagnosed PACG, uveal effusion was found in 4 of 28 eyes (14.2%; 95% confidence interval, 5.1%-32.1%) before laser iridotomy; 2 eyes had effusion after laser iridotomy. When present, the effusion was grade 1 in PACG eyes and grade 2 or 3 in APAC eyes.

Conclusions: Uveal effusion was present in a significant proportion of Asian eyes with PACG and APAC, confirming a recent report of this finding.

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Uveal (ciliochoroidal or choroidal) effusion is an abnormal accumulation of fluid in the suprachoroidal space that has been previously observed in eyes with nanophthalmos. Uveal effusion also has been found when intraocular pressure (IOP) is either very low, such as after trabeculectomy, or high, such as during an episode of acute primary angle closure (APAC). Recently, Quigley et al proposed that choroidal expansion may precede and even precipitate angle closure. It was hypothesized that under normal circumstances an increase in choroidal volume would result in increased aqueous flow so that there is no shift in the lens or iris position, but since the vitreous has a limited capacity to transmit fluid, there can be anterior movement of the compressed vitreous, iris, and lens when transvitreous flow is not enough. In small eyes predisposed to angle closure, choroidal expansion, leading to increased vitreous cavity pressure, might be a contributing cause. Sakai et al investigated the prevalence of uveal effusion using ultrasound biomicroscopy (UBM) in 501 Japanese patients with primary angle closure. This sample included 70 patients with treated APAC and 431 patients with chronic primary angle closure (PAC). The authors found uveal effusion in 9% of eyes with chronic PAC, 58% of eyes with APAC, and 23% of fellow eyes with APAC. The authors also reported a 2% prevalence of uveal effusion in their control group (primary open-angle glaucoma eyes) and found shallower anterior chamber depth in chronic PAC eyes with uveal effusion compared with eyes without effusion.

In this study, we attempted to confirm the findings by Sakai et al of uveal effusion using UBM in 3 groups of patients: a first group composed of a sample of patients with newly diagnosed primary angle closure glaucoma (PACG) who were investigated using UBM before and after laser iridotomy (LI), a second group composed of patients with PACG who were being monitored after previous LI, and a third group of patients with APAC.

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METHODS

This was a prospective, observational study of consecutive patients older than 40 diagnosed as having PACG or APAC at the Singapore National Eye Center. Written informed consent was obtained from all study participants, and the study protocol had the approval of the hospital's ethics committee and was performed according to the tenets of the Declaration of Helsinki.

All patients underwent an ophthalmic examination, including visual acuity testing, axial length and central anterior chamber depth (ACD) measurement (IOL Master; Carl Zeiss Meditec, Dublin, California), IOP measurement with Goldmann applation tonometry, visual field testing (Humphrey Visual Field Analyzer II using the SITA standard algorithm with a 24-2 test pattern; Carl Zeiss Meditec), and fundus examination. Static and dynamic gonioscopy was performed in the primary position of gaze under the lowest level of ambient illumination that permits a view of the angle and at high magnification (>25). The angle was graded using the Scheie grading system, which is based on the anatomical structures observed during gonioscopy.\(^1\) Static gonioscopy was performed using a Goldmann 2-mirror lens. Dynamic (indentation) gonioscopy was performed on all study participants using a Sussman 4-mirror gonioscope to determine the presence or absence of peripheral anterior synechiae (PAS).

Three subgroups of patients were studied. Group 1 was patients with newly diagnosed PACG who were enrolled before LI or commencement of any medical therapy. For these patients, UBM was performed before and then repeated approximately 2 weeks after LI. Primary angle closure glaucoma (PACG) was defined as the presence of glaucomatous optic neuropathy (defined as loss of neuroretinal rim with a vertical cup: disc ratio of ≥0.7 or with notching of the optic disc) with compatible visual field loss in association with a closed angle (presence of at least a 180° angle in which the trabecular meshwork was not visible on nonindentation gonioscopy) and raised IOP and/or PAS. The second group was patients with previously diagnosed PACG who were being followed up in the clinics (these eyes had previously undergone LI); these patients underwent UBM at enrollment. The third group was patients with APAC (defined as the presence of the following symptoms and physical observations: ocular and/or periocular pain, nausea and/or vomiting, blurred vision, IOP >30 mm Hg, conjunctival hyperemia, corneal epithelial edema, mid-dilated pupil, and bilateral shallow anterior chamber with closed angles). The UBM was performed in these eyes before any treatment and again 1 to 2 weeks after LI; we did not perform UBM in the fellow eyes to minimize patient discomfort.

Ultrasound biomicroscopy was performed in dark room conditions using a 50-MHz transducer (Paradigm Medical Industries, Salt Lake City, Utah). A single experienced observer (R.S.K.) performed all UBM scans. Patients were examined while in the supine position, and radial scans were performed in the inferior, temporal, superior, and nasal quadrants. The probe was held perpendicular to the ocular surface, such that the scleral spur, and the ciliary body and angle were visualized. To detect uveal effusion, UBM was performed as posteriorly as possible beyond the scleral spur. To evaluate for circumferential extension of effusion, the examiner performed multiple scans in the 4 primary quadrants (3-, 6-, 9-, and 12-o’clock positions) and in areas between these quadrants. In patients who had bilateral PACG, one eye was randomly chosen as the study eye and UBM was performed in that eye only.

Uveal effusion was defined as a clear space (hypoechoicogenic lines) between the choroid and sclera up to the equator on radial scans. Grading of the effusion was performed based on the previous report by Sakai et al.,\(^1\) using photographs as a reference: grade 0, none; grade 1, slitlike (supraciliary space less than half the ciliary body thickness); grade 2, bandlike (supraciliary space greater than half the ciliary body thickness); and grade 3, obvious (supraciliary space greater than the ciliary body thickness). Grading was performed by looking at the images on a personal computer using UBM Pro 2000 (Paradigm Medical Industries), while comparing each image with the standard set of images. The UBM images that showed uveal effusions were reevaluated and confirmed by a second observer with extensive experience in this area (H.S.).

The intraobserver reproducibility for the assessment of uveal effusion in UBM images was assessed in a randomly selected subset of 50 patients (50 eyes). Images were graded for the presence of uveal effusion in 2 sessions separated by an interval of 1 week by a single examiner (R.S.K.) masked to other results.

Statistical analysis was performed using MedCalc software (Mariakerke, Belgium). Parametric and nonparametric tests were used to compare continuous variables, according to data distribution. The \(\chi^2\) test was used to compare categorical data. Intraobserver reproducibility for identifying uveal effusion was assessed using the AC1 test.\(^1\)

RESULTS

Of the 82 patients enrolled in the study, 28 had newly diagnosed PACG, 42 patients with PACG had undergone prior LI and were being monitored, and 12 had APAC. Most patients were Chinese (89.3%); the rest were Indians (5.3%) and Malays (5.4%). Demographic and clinical characteristics of these patients are summarized in Table 1. No significant difference was found in terms of ACD or axial length between the eyes of patients with PACG and those with APAC; however, those patients with APAC were younger and had less optic disc cupping compared with the patients with PACG (Table 1). The IOP was also significantly different among the 3 groups because the patients with APAC and newly diagnosed PACG were not treated before enrollment, whereas many patients with previously diagnosed PACG were receiving treatment (Table 1).

Overall, uveal effusion was found in 11 of 70 eyes with PACG (15.7%; 95% confidence interval [CI], 8.8%-26.2%). Of the 28 patients with newly diagnosed PACG, uveal effusion was noted in 4 of 28 eyes (14.2%; 95% CI, 5.1%-32.1%) before LI. After LI, only 2 of these eyes (7.1%; 95% CI, 0.9%-23.7%) demonstrated effusion. Among patients with PACG who had undergone LI previously and were being monitored, uveal effusion was seen in 7 of 42 eyes (16.6%; 95% CI, 8.0%-30.9%). For this group, the median interval between LI and UBM examination was 16 months (range, 2-86 months); 30 of these 42 eyes (71.4%) had been treated with at least 1 medication at the time of UBM. Of the 7 eyes that had effusion, 6 eyes were being treated with topical IOP-lowering medications (1 eye did not require medications to control IOP); 5 of 6 eyes were being treated with prostaglandin analogs (10/42 eyes to which prostaglandins were applied did not demonstrate effusion). All the uveal effusion found in the 11 patients with PACG were grade 1 effusion (Figure 1). No difference was found in demographic features or biometry in PACG eyes with and without uveal effusion (Table 2).

In patients with APAC, 3 of 12 eyes (25.0%; 95% CI, 8.0%-53.4%) demonstrated uveal effusion. Two eyes dem-
onstrated grade 2 effusion, whereas the other showed grade 3 effusion (Figure 2). None of these eyes demonstrated effusion after LI.

We did not find effusion extending beyond the equator except in the 3 eyes with APAC. Regarding the circumferential extent of effusion, in patients with newly diagnosed PACG, 3 of 4 eyes showed effusion in 2 quadrants, whereas 1 eye had effusion extending to 3 quadrants. In the chronic PACG group, 6 of 7 eyes showed effusion extending to 2 quadrants, whereas 1 eye had effusion in 3 quadrants. In 2 of 3 eyes with APAC, effusion extended to 2 quadrants; the other eye had effusion extending to 3 quadrants. Effusion was most common in the inferior quadrant (10/11 PACG eyes, 90.9%) followed by the temporal quadrant (6/11 eyes, 54.5%), nasal quadrant (5/11 eyes, 45.5%), and superior quadrant (3/11 eyes, 27.3%). In the APAC group, the inferior quadrant showed effusion in all 3 eyes, and there was 1 case each of effusion in the superior and nasal quadrants.

We also found that effusion was common in quadrants with PAS; 18 of the 24 quadrants (overall) that had uveal effusion had at least 1 clock hour of PAS; in 2 instances, the quadrant had 3 clock hours of PAS. The results of the AC1 test showed that intraobserver reproducibility for identifying uveal effusion in PACG eyes was excellent (AC1 = 0.82).

**COMMENT**

In this study, we found that, overall, approximately 15% of PACG eyes had uveal effusion on UBM. We studied eyes with newly diagnosed PACG before any initiation

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Patients With Newly Diagnosed PACG (Group A) (n=28)</th>
<th>Patients With Previously Diagnosed PACG (Group B) (n=42)</th>
<th>Patients With APAC (Group C) (n=12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) [range], y</td>
<td>67.3 (7.5) [55-90]</td>
<td>68.4 (7.1) [48-83]</td>
<td>61.1 (7.4) [48-73]</td>
<td>.31 (A and B); .03 (A and C); .004 (B and C) a</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 12 Female 16</td>
<td>Male 15 Female 27</td>
<td>Male 5 Female 7</td>
<td>.80 b</td>
</tr>
<tr>
<td>Axial length, mean, mm (95% confidence interval)</td>
<td>22.83 (22.40-23.27)</td>
<td>23.20 (21.35-25.92)</td>
<td>22.43 (21.67-23.18)</td>
<td>.41 (A and B); .32 (A and C); .08 (B and C) a</td>
</tr>
<tr>
<td>Anterior chamber depth, mean, mm (95% confidence interval)</td>
<td>2.55 (2.45-2.65)</td>
<td>2.61 (2.50-2.71)</td>
<td>2.54 (2.01-3.07)</td>
<td>.61 (A and B); .20 (A and C); .12 (B and C) a</td>
</tr>
<tr>
<td>Intraocular pressure, mean, mm Hg (95% confidence interval)</td>
<td>25.7 (21.4-29.9)</td>
<td>17.3 (15.9-18.6)</td>
<td>46.6 (40.9-52.2)</td>
<td>&lt;.001 (A and B); &lt;.001 (A and C); &lt;.001 (B and C) a</td>
</tr>
<tr>
<td>Vertical cup-disc ratio, mean (95% confidence interval)</td>
<td>0.79 (0.75-0.84)</td>
<td>0.77 (0.50-0.95)</td>
<td>0.52 (0.37-0.65)</td>
<td>.56 (A and B); &lt;.001 (A and C); &lt;.001 (B and C) a</td>
</tr>
</tbody>
</table>

Abbreviations: APAC, acute primary angle closure; PACG, primary angle closure glaucoma.

a Mann-Whitney test.
b χ² test.

Figure 1. Radial ultrasound biomicroscopy images of an eye with newly diagnosed primary angle closure glaucoma. Images were taken before (A) and after (B) laser iridotomy. Grade 1 uveal effusion was noted at both time points (arrows). S indicates sclera; C, choroid; I, iris; and CB, ciliary body.
of treatment and found that 4 of 28 such eyes (14.2%) had uveal effusion, but after 2 weeks only 2 of 28 eyes were found to have effusion. In the other subgroup of PACG eyes that had undergone LI previously and were being monitored, 15% were also found to have uveal effusion on UBM. Among patients with APAC, 3 of 12 eyes (25.0%) demonstrated uveal effusion.

The findings of uveal effusion in untreated eyes with PACG or APAC before LI are novel and have not been reported previously. We cannot explain the reason for the presence of uveal effusion in these eyes, and it is not known if uveal effusion is a cause or effect of PACG or APAC. Liebmann et al previously reported such effusions as a cause of postoperative angle closure glaucoma. Quigley et al proposed several contributing risk factors for PACG and APAC: small eye size, choroidal expansion, and poor vitreous conductivity. They suggested that choroidal expansion might be present before and be a contributory factor to APAC and that this expansion may be due to an increase in the volume of the extravascular choroid space. Quigley et al also suggested that the lens moves forward anteriorly because of this expansion and, if this expansion occurs in an intact eye, the natural outcome would be increased IOP. In other words, an increase in choroidal volume would increase IOP coincident with the expansion and, as aqueous humor leaves the anterior chamber, a pressure differential would develop between the vitreous cavity and posterior chamber on the one hand and the anterior chamber on the other. This may worsen the pupil block whether the lens moves forward or not; it is possible that in some cases the iris would bow forward more than the lens.

In our series, only 25% of eyes with APAC had uveal effusion compared with 58% in the study by Sakai et al, although this may be an effect of our small sample size. Previous reports have been made of choroidal detachment with suprachoroidal fluid in eyes with APAC. Gazzard et al used UBM and reported suprachoroidal fluid collection in a series of patients with APAC. In these patients, the effusion resolved spontaneously in 5 days. There also have been reports of suprachoroidal fluid being present before acute attacks. Gazzard et al suggested that it was possible that their series of patients had preexisting transient albeit small idiopathic effusions. Yang et al investigated the short-term changes in biometry in 41 Asian eyes with APAC. They did not find any significant changes in ACD, lens position, or relative lens position before and after LI, suggesting lack of evidence to support the hypothesis of anterior lens movement secondary to choroidal expansion as a possible mechanism for APAC.

Various other mechanisms have been suggested for accumulation of suprachoroidal fluid: sudden decrease (or increase) in IOP, exudation from uveal vessels, congestion of choroidal circulation due to high IOP, and the effect of topical pilocarpine hydrochloride and oral acetazolamide sodium. Sudden reduction of IOP associated with choroidal detachment also has been reported after trabeculectomy and bleb needling. The choroid may separate from the sclera because of fluid accumulating in the suprachoroidal space at a rate faster than it can drain; this could occur as a result of increased vascular permeability (inflammation or neoplasia), increased intravascular pressure (nanophthalmos or uveal effusion syndrome), or lowering of IOP that causes reduction of hydrostatic pressure gradient, thus decreasing outflow.

Sakai et al reported that eyes that had uveal effusion had shallower anterior chambers compared with those without effusion. In our series, no significant difference was found in ACD between those who had effusion and those who did not. Sakai et al also found that most (34/39, 87%) of the chronic PAC eyes had grade 1 effusion and 5 of 39 eyes had grade 2 effusion. We found that the effusion in PACG eyes when present in our series was grade 1; we do not know if this was because of the smaller...
sample size or that the mean (SD) ACD of the PACG eyes in our series (2.62 [0.25] mm) was significantly more than that in the study by Sakai et al (1.99 [0.36] mm) (P < .001). Six of the 7 patients with PACG who were being monitored had effusion were taking medications; 5 were taking prostaglandins. We believe that the sample is too small to comment on the relevance of prostaglandin treatment as a causal factor for uveal effusion because such information could merely reflect the current trend of treatment with this class of drugs. Interestingly, all 3 of our APAC eyes with uveal effusion had grade 2 or 3 effusions.

Our study had a few limitations. Many eyes with previously diagnosed PACG were undergoing medical therapy, which may have affected the prevalence of uveal effusion. In patients with newly diagnosed PACG, we could not establish the temporal sequence of the changes in uveal effusion because we did not perform serial UBM in the early post-LI period, and the reproducibility of effusion at different time points was not investigated. Our relatively small sample of patients with PACG and APAC might have limited the interpretation of the results of this study. We did not measure the sclera or ciliary body thickness in eyes that had effusion, which might have provided information on whether a thicker sclera or ciliary body predisposes patients to higher risk of uveal effusion. Finally, there was no control group to determine whether effusion might be present in normal eyes as well (Sakai et al reported a 2% prevalence of effusion in primary open-angle glaucoma eyes).

An experienced examiner (R.S.K.) performed all UBM scans in this study, which would have reduced the chances of the waterbath pressing down on the eye, thereby obstructing venous outflow from the vortex veins and artificially producing effusions. We performed transverse scans in some of the eyes and found that if the effusion was identifiable in axial scans, it was reproducible on transverse scans as well. We could not demonstrate circumferential effusion in all 4 quadrants of any eye, which could be due to a limitation of the UBM in identifying effusion only after a certain amount has accumulated. The artificial grading system that was used in this study probably does not indicate the levels to which the choroids need to be swollen to contribute to angle closure disease; more precise methods to measure uveal effusion are required.

In conclusion, we found subclinical uveal effusion in patients with newly diagnosed untreated PACG both before and after LI, with resolution of effusion after LI in some cases. The clinical implications of this finding are not fully understood. Our findings indicate that the prevalence of uveal effusion was similar in untreated and in previously treated patients with PACG. We also found uveal effusion in 25% of patients with APAC. To our knowledge, this is the first study to confirm the findings by Sakai et al of the presence of uveal effusion in eyes with PACG or APAC. Detection of effusion using UBM may be potentially used as a predictive test in anatomically small eyes and gonioscopically narrow angles to determine those that are at a higher risk of developing angle closure and/or glaucoma. Additional longitudinal studies would be helpful in elucidating the role of uveal effusion in the pathogenesis of PACG and investigating the effects of medical, laser, or surgical treatments on this finding.

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