In Vivo Analysis of Angle Dysgenesis in Primary Congenital, Juvenile, and Adult-Onset Open Angle Glaucoma

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The conventional outflow system (i.e., trabecular meshwork [TM] and the Schlemm’s canal [SC]) is believed to be the site of major glaucomatous pathobiology as it can offer significant anatomic and functional obstruction to outflow. Also, pathologic changes to SC may create significant aqueous outflow resistance; hence, considerable interest is being given to characterize and evaluate the SC as a target for glaucoma therapeutics.

Spectral domain–optical coherence tomography (SD-OCT) is being increasingly used to assess the anterior chamber angle in glaucoma patients. It has, however, been used primarily to look into the angle recess in patients with angle closure disease.1–4 With the current high definition anterior segment OCT, interest has been generated in visualizing the TM and SC in vivo.5–8

Primary congenital glaucoma, juvenile-onset open angle glaucoma, and high-pressure adult-onset open angle glaucoma are considered a continuum with varying severity of abnormalities in the TM. Developmental glaucomas, such as primary congenital glaucoma (PCG) and juvenile-onset open angle glaucoma (JOAG), are known to have anomalies in the angle that manifest as goniodysgenesis and are the cause of glaucoma at an early age in life. Urbak, in 1999, analyzed the angle in JOAG eyes using ultrasound biomicroscopy (UBM) but could not find any changes of angle dysgenesis on UBM despite gonioscopic evidence of dysgenesis in these eyes.9

The purpose of this study was to comparatively evaluate angle dysgenesis in vivo, among congenital, juvenile, and adult-onset open angle glaucoma patients.

Methods. A cross-sectional evaluation of 96 glaucoma patients, 22 children with primary congenital glaucoma (PCG) old enough to cooperate for optical coherence tomography (OCT), 34 juvenile-onset open angle glaucoma (JOAG) patients, 40 adult-onset primary open angle glaucoma (POAG), and 30 healthy subjects, was carried out using high-resolution anterior segment spectral domain (SD)-OCT. Subgroup analysis was done for presence/absence of angle dysgenesis as defined by presence of abnormal tissue/hyperreflective membrane within angle recess and/or absence of Schlemm’s canal (SC).

Results. Morphologic features suggestive of angle dysgenesis such as the presence of abnormal tissue at the angle and a hyperreflective membranous structure covering the meshwork were seen in all PCG eyes (100%), in 14 (40%) JOAG eyes, and none of the POAG eyes in comparison to healthy eyes (P = 0.01, P = 0.03, and P = 0.23 for PCG, JOAG, and POAG, respectively). SC could be seen in 27 (90%) healthy eyes compared with only 7 (30%) in PCG (P = 0.01) 20 (60%) JOAG eyes (P = 0.03), and 26 (65%) adult-onset POAG eyes (P = 0.25; χ² test).

Conclusions. Angle dysgenesis in the form of abnormal tissue at the angle/hyperreflective membrane and/or absence of SC could be identified on anterior segment SD-OCT, which can be used for in vivo evaluation of eyes with developmental glaucoma.

Keywords: angle dysgenesis, congenital glaucoma, juvenile glaucoma

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Inclusion criteria for PCG were as follows: treated/operated cases of PCG with enlarged corneal diameters (>12 mm) who had baseline IOP records of >22 mm Hg detected before 3 years of age and were now old enough (>10 years of age) to cooperate for anterior segment OCT scanning.

**Adult-Onset POAG**

These were unrelated cases of POAG patients diagnosed after the age of 40 years with untreated IOP ≥22 mm Hg in one or both the eyes on more than two occasions, open angle on gonioscopy in both eyes, and glaucomatous optic neuropathy in one or both eyes with visual field loss consistent with optic nerve damage. Only those eyes that had not undergone previous surgery were included.

**JOAG Patients**

These were unrelated POAG patients diagnosed between 10 and 40 years of age. Only those eyes that had not undergone previous surgery were included.

Patients excluded from the study: those with a history of steroid use, presence of any other retinal or neurologic pathology, evidence of secondary causes of raised IOP such as pigment dispersion, pseudoxefoliation, or trauma, those with any pathology detected on gonioscopy such as angle recession, pigmentation of the angle greater than grade 3, irido trabecular contact or peripheral anterior synchia, and patients with nystagmus were excluded. Those eyes with advanced glaucoma or poor visual acuity that precluded a proper fixation for examination were also excluded.

A detailed history was taken and an examination was performed for all individuals included in the study. All patients underwent gonioscopy by an experienced glaucomatologist for future reference. Images were captured at optimum illumination and stored in the Eye Cap system (Haag Streit International, Koeniz, Switzerland), which is a digital photographic system attached to the slit lamp.

The OCT examination was performed using the Spectralis OCT (software version 6.5; Heidelberg Engineering GmbH, Heidelberg, Germany). This machine uses an 880-nm wavelength and provides a resolution of 3.5 μm (digital) to 7 μm (optical) at 40 kHz. An anterior segment lens was used. The angle was imaged taking horizontal sections (at 3 and 9 o'clock). Instead of the angle module of the Spectrals, we used the Scera module to get dense scans of high resolution. The machine provided 49 scans with a distance of 35 μm between two scans. Horizontal scans were taken without elevating the lid and thereby avoiding globe compression. The automated real-time (ART) scan was adjusted between 80 and 100 frames. Only those images that were considered good quality were included. Both eyes of the subjects were imaged, and the right eye images of all patients were used for analysis. Among patients with unilateral glaucoma, the images of eye with glaucoma were analyzed.

Two glaucoma specialists, masked to the demographic profile of the patients and the clinical diagnosis, evaluated the OCT images with regards to angle dysgenesis (identification of the presence or absence of a hyperreflective membrane/abnormal tissue at the angle) and commented on the presence or absence of SC (as yes or no). If the SC or a hyperreflective membrane/abnormal tissue at the angle was seen in any of the scans, it was considered observable for the purpose of analysis. In cases of disagreement between the two observers, a third glaucoma specialist adjudicated the case.

**Statistical Analysis**

To compare the baseline variables (clinical and demographic), we used the independent t test for continuous variables and a χ² test for categorical variables. The χ² test was used to compare the presence and absence of angle dysgenesis among the different groups. All analyses were performed using a statistical software package (SPSS for Windows, v. 17.0; SPSS, Inc., Chicago, IL, USA). To determine the agreement between the two specialists, Cohens k test was applied. P < 0.05 was considered significant.

**RESULTS**

In this study, 126 consecutive subjects who met the study criteria were included. The clinical and demographic characteristics of these are shown in Tables 1 and 2. There were 880 images (on average, 6.8 ± 2.3 images per subject) that were provided to two masked glaucoma specialists for evaluation. The agreement between the specialists for being able to identify SC was higher (κ = 0.76, P < 0.001) than for identifying abnormal angle tissue/membrane at the angle (κ = 0.61, P < 0.005). Overall, the SC could be identified in 65% eyes, and abnormal tissue/hyperreflective membrane at the angle was seen in 40% eyes.

**Morphologic Assessment of the Angle in Different Subgroups (Table 3)**

**Healthy Eyes.** Abnormal tissue/hyperreflective membrane at the angle was not seen in any of the eyes that were healthy, and the SC could be identified in 27 (90%) eyes (Fig. 1).

**POAG.** Abnormal tissue/hyperreflective membrane at the angle was not seen in any of the POAG eyes, and SC could be identified among 26 (65%) of the adult-onset POAG eyes (Fig. 2).

**JOAG.** In 14 (40%) JOAG eyes, there were features of abnormal tissue/hyperreflective membrane at the angle, and SC could be identified in 20 (60%) JOAG eyes (Figs. 3A, 3B).

**PCG.** All eyes had evidence of either an abnormal tissue over the angle (Figs. 4A, 4B) or the presence of a hyperreflective membrane (Fig. 5). The SC could be identified in only seven (30%) eyes. In a child with unilateral PCG, one could see the abnormal tissue at the angle and lack of SC in the left eye that had PCG compared with the normal right eye (Fig. 6).
6). All eyes with PCG had undergone a superior trabeculectomy with trabeculotomy, which is the standard surgical procedure undertaken for control of IOP in these patients at our institute. None of these children had undergone a goniotomy.

**DISCUSSION**

SD-OCT provides high-resolution assessment of the angle structures. Using Heidelberg Spectralis, which has an axial resolution of approximately 7 to 10 μm, we could capture good images that revealed angle dysgenesis in a substantial proportion of PCG and JOAG eyes.

The dysgenesis was seen either as the presence of abnormal tissue or a hyperreflective membrane. This membrane appeared to be like what Barkan described in PCG and was later commented on by Luntz as an angle cicatrization that portends poorer success with goniotomy. In our study, the agreement between two glaucoma specialists regarding the presence or absence of dysgenesis was only moderate. This is expected in the absence of existing literature on morphologic identifiers of angle dysgenesis on anterior segment OCT.

Goniodysgenesis has been described not only in congenital and juvenile glaucomas but also among high-pressure adult-onset glaucomas. The spectrum of abnormalities is more severe in PCG than juvenile glaucomas. In a previous study, we tried to relate the goniodysgenesis as evaluated by goniophotography with the clinical manifestation of the disease among 126 JOAG patients. We found that the presence or absence of goniodysgenesis among JOAG patients did not correlate with the age at presentation or the highest untreated IOP. It is known that gonioscopy provides only a superficial representation of the histopathologic anomalies affecting the angle. Tawara and Inomata observed the presence of a thick compact tissue in the TM samples of juvenile glaucoma patients, irrespective of whether they had an apparent goniodysgenesis or not. Hence, what appears to be morphologically normal angle on gonioscopy may harbor dysgenesis of the TM or even the SC. This can only be revealed either by histopathologic examination or with the help of in vivo high definition imaging of the angle. In fact, in eyes with angle dysgenesis on gonioscopy, the severity of dysgenesis could actually be more than is evident en face on gonioscopy.

Identification of the SC has also been made possible with the new-generation anterior segment optical coherence tomography (ASOCT) devices. A reasonably good agreement was seen between the two glaucoma specialists in their ability to identify the SC. Our study failed to show a discernible SC in majority of PCG and JOAG eyes, whereas it was present in most of the healthy subjects. Asrani et al. reported visualization of SC among angle closure glaucoma patients using the swept-table 2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PCG</th>
<th>JOAG</th>
<th>Adult-Onset POAG</th>
<th>Normal Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of SC (%)</td>
<td>15 (70%)</td>
<td>14 (41%)</td>
<td>14 (35%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>P value ($\chi^2$ test)</td>
<td>0.01*</td>
<td>0.05*</td>
<td>0.23*</td>
<td></td>
</tr>
<tr>
<td>Presence of abnormal tissue/hyperreflective membrane (%)</td>
<td>22 (100%)</td>
<td>14 (40%)</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>P value ($\chi^2$ test)</td>
<td>0.001*</td>
<td>0.02*</td>
<td>0.56*</td>
<td></td>
</tr>
</tbody>
</table>

* Comparison with controls.
† Comparison with JOAG.
‡ Comparison with POAG.

![Figure 1](http://arvojournals.org/)

**Figure 1.** Angle of a healthy person showing the extent of SC as white arrows surrounding the TM.

![Figure 2](http://arvojournals.org/)

**Figure 2.** Angle of a POAG patient showing a prominent SC marked by arrows posterior to the TM.
source fourier domain optical coherence tomography (FDOCT). SC has been shown to be observable on ASOCT among healthy subjects in 85% to 90% cases. Lack of proper development of the SC has been postulated in the pathogenesis of primary congenital glaucoma. However, Rojas et al. showed the presence of SC in two histopathologic samples of TM in congenital glaucoma eyes. Lack of SC was also shown by Hollander et al. to be associated with a severe form of goniodysgenesis, whereas its presence was seen in less severe goniodysgenesis. Tandon et al., in a recent ultrasound biomicroscopic study, also failed to identify the SC in 50% of the eyes of children with congenital glaucoma. One can postulate that eyes with abnormal tissue/hyperreflective membrane at the angle with concomitant absence of SC could be considered to have a more severe form of angle dysgenesis.

The size of the SC has also shown to be decreased in patients with adult-onset open angle glaucoma in both histopathologic and in vivo OCT studies. Johnson et al. reported that, in enucleated human eyes, those with glaucoma exhibited only 20% of the intracellular and border pore density in SC endothelium compared with normal eyes. Similarly, Overby et al. suggested that pore formation correlated with the stiffness of SC cytoskeletal cells and that the SC cells of glaucomatous eyes exhibited both a stiffer cytoskeleton with a reduced ability to form intra and transcellular pores. Consequently, these findings again reflect a high incidence of pathologic alterations within the SC in the development of glaucoma. Some consider a decrease in the SC size to be a consequence of raised IOP. In our study, all patients had well-controlled IOP prior to the anterior segment imaging.

From this relatively large number of eyes with developmental glaucomas showing absence of SC, we may infer that SC plays a greater role in the pathogenesis of congenital and juvenile glaucoma. Being an in vivo evaluation, our study would not have the artifacts induced by tissue dissection and processing that were inherent in earlier histopathologic studies. A larger number of cases of developmental glaucomas imaged with ultra-high-resolution OCT may further substantiate our results. Also comparing the eyes of children with unilateral congenital glaucoma using anterior segment OCT, could help pick up the causes of development of glaucoma in one eye in comparison to the other, especially when both eyes show similar gonioscopic abnormalities.
One of the strengths of the study is that the resolution of the images and their quality is superior compared with those from previous studies acquired on the RTvue (Optovue, Inc., Fremont, CA, USA). However, some features that limit the identification of angle structures, like the lack of a clear demarcation of Schwalbe’s line and scleral spur on the OCT images, makes it difficult to clearly identify the extent of the TM. Moreover, the SC identification itself may vary depending on the area scanned.6 Another limitation of the study is that we included cases of PCG that had been operated before. There is a possibility that the anatomy of the SC may alter after undergoing trabeculectomy. Hong et al. have shown that trabeculectomy widens the SC, and the degree of expansion is correlated with the lowering of IOP.30 However, we could not identify SC in the majority of the eyes of PCG patients, even though they had been operated for trabeculectomy and despite the fact that we were able to acquire scans of high resolution. Interestingly, we found differences between two eyes in one PCG patient with unilateral glaucoma where SC was visible in the normal (healthy) eye but not in the eye with congenital glaucoma that had been operated (Fig. 6). More studies on such unilateral cases would better elucidate developmental abnormalities of the angle using OCT.

Regarding the developmental immaturity of the angle, it is difficult to ascertain what is normal or abnormal as there is a large anatomical variability in the TM morphology even among normal individuals. This could be one of the reasons of getting only a moderate agreement between the two observers with regard to angle dysgenesis. The definition for angle dysgenesis on OCT used in this study is an oversimplification of a complex process of development. Other features like a lack of a rarefied TM or an increased density of tissue in the area of TM are some other subtle characteristics of angle abnormalities that need to be looked into carefully in future studies. Even different parts of the angle in the same eye may show areas of more severe angle dysgenesis compared with others. For the purpose of this study, only horizontal cross-sectional scans through 3 and 9 o’clock meridians were used for analysis. However, a high-definition swept-source analysis of 360°, in the future, would add value to the inference made. Although there is limited literature on this subject, it is gaining interest with the advent of high definition OCT devices. The identification of angle dysgenesis in vivo may be correlated with the clinical severity of different types of glaucomas, especially the congenital and developmental variants, and this could be elicited in a future study. High-resolution portable OCT devices developed in future may also aid in identification of angle dysgenesis in glaucomatous eyes of children.

This study illustrates the usefulness of anterior segment OCT in identifying angle dysgenesis and its prevalence in various open angle glaucomas. With advances in OCT technology and the advent of higher-resolution capture, in-depth morphologic analysis of angle may be possible with higher precision. Morphologic characterization of the trabecular anatomy, as well as that of SC, may then be applied to choose an appropriate surgical modality for treatment of developmental glaucomas.

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References


