Evaluation of Anterior Lenticonus in Alport Syndrome Using Tracey Wavefront Aberrometry and Transmission Electron Microscopy

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BACKGROUND AND OBJECTIVE: To evaluate the efficacy of Tracey wavefront aberrometry (Tracey Technologies, Houston, TX) and transmission electron microscopy for the detection of anterior lenticonus in Alport syndrome.

PATIENTS AND METHODS: Tracey wavefront aberrometry was used to treat a patient with bilateral anterior lenticonus who had a history of Alport syndrome. For transmission electron microscopic examination, anterior lens capsules were obtained during clear lens phacoemulsification and intraocular lens implantation.

RESULTS: Spherical aberrations were the predominant higher-order aberrations in the internal optics of both eyes. The Tracey wavefront aberrometer showed that most of the irregular astigmatism originated from the lenticular portion. Transmission electron microscopy of the specimens showed anterior lens capsules with decreased thickness and multiple dehiscences.

CONCLUSION: Tracey wavefront aberrometry and transmission electron microscopy are effective tools for evaluation of anterior lenticonus in Alport syndrome.


INTRODUCTION

Alport syndrome is an inherited disorder characterized by progressive nephropathy with basement membrane structural defects, sensorineural hearing loss, and frequent ocular abnormalities. It is characterized by X-linked, autosomal recessive or autosomal dominant inheritance, but 85% of cases have been reported to be associated with X-linked inheritance. The responsible mutations affect the COL4A5 gene for the α5 chain of type IV collagen, which is the major constituent of the basement membrane in the glomerulus, cochlea, retina, lens capsule, and cornea.1
The reported incidence of ocular manifestations in Alport syndrome ranges from 11% to 92%. Ocular manifestations are characterized by retinal flecks, anterior lenticonus, cataracts, corneal arcus, recurrent corneal epithelial erosion, and corneal dystrophies. Arnott et al. reported that anterior lenticonus is a specific sign for Alport syndrome. In some reports, more than 90% of cases of anterior lenticonus were associated with Alport syndrome. Anterior lenticonus may lead to progressive visual loss as a result of either irregular astigmatism or cataract formation. Crystalline lens phacoemulsification is often indicated in patients with Alport syndrome because of progressively decreased visual acuity.

The diagnosis of anterior lenticonus is based on findings on slit-lamp biomicroscopy. The findings of abnormal lens contour on slit-lamp examination and normal corneal topography strongly suggest lenticular irregular astigmatism. A scissors reflex is often found in both eyes, resulting in the oil droplet appearance that is associated with anterior lenticonus. However, these methods provide no quantitative analysis for lenticular irregular astigmatism. Recently, it became possible to measure the lenticular portion of an irregular astigmatism indirectly by subtracting the corneal irregular astigmatism measured with corneal topography from the irregular astigmatism of the entire eye measured with wavefront analysis.

The current study evaluated irregular astigmatism of the lens and entire eye of a patient with Alport syndrome using a Tracey wavefront aberrometer (Tracey Technologies, Houston, TX) and described the results of histologic evaluation of the lens capsules acquired intraoperatively using transmission electron microscopy to clarify the underlying pathology.

**Patients and Methods**

A 25-year-old man was diagnosed as having Alport syndrome. He had a history of progressive bilateral decreased visual acuity beginning 5 years before he was seen in our clinic. He also had a history of recurrent episodes of nontraumatic corneal erosion. He first noticed dark urine at 6 years of age and had progressed to end-stage renal disease resulting in hemodialysis. He had had sensorineural hearing loss since childhood.

Family history showed that his mother had died of renal disease.

**Preoperative and Postoperative Examinations**

Preoperatively, best-corrected visual acuity (BCVA), intraocular pressure, and manifest refraction were recorded in both eyes. Anterior segment and fundus examinations were also performed. Initial slit-lamp examination showed loose epithelium and corneal erosion in the right eye and a large corneal epithelial defect in the left eye. Artificial tears, autologous serum, and therapeutic contact lenses were applied to control the recurrent corneal epithelial defects in both eyes. After the corneal surface had been stabilized, corneal topography (ORBscan II; Bausch & Lomb-Orbtek Inc., Salt Lake City, UT) and Tracey wavefront aberrometry were used to measure the irregular astigmatism in the central 6.0-mm zone. Two years after the lens surgery, corneal topography and wavefront measurements were performed again to evaluate changes.

**Surgical Procedures**

Both eyes underwent conventional coaxial clear lens phacoemulsification through a 2.75-mm temporal corneal wound construction with a continuous curvilinear capsulorhexis and hydrophobic acrylic spherical foldable intraocular lens (IOL) implantation (Sensar; Abbott Medical Optics, Abbott Park, IL). Capsulorhexised anterior lens capsules were removed from the anterior chamber and divided into two portions, central and peripheral. Those specimens were fixed in 2.5% glutaraldehyde for transmission electron microscopic examination. There were no intraoperative complications. The patient gave informed consent before participation in the study. The approval of the institution’s investigational review board was obtained.
Initial BCVA was 20/50 sphere -6.0 cylinder -3.5 × 5 in the right eye and 20/200 sphere -10.0 cylinder -4.5 × 165 in the left eye. Slit-lamp examination after pupil dilation showed anterior lenticonus characterized by centrally protruding anterior capsules in both eyes (Fig. 1). Fundus examination showed small, circumscribed white dots in the perimacular area in both eyes. After clear lens phacoemulsification, a recurrent epithelial defect was detected in the right cornea. Artificial tears, autologous serum, therapeutic contact lenses, and anterior stromal puncture were applied to stabilize the epithelium. Two years after clear lens phacoemulsification and IOL implantation, BCVA was 20/20 cylinder -2.0 × 5 in the right eye and 20/200 sphere +1.0 cylinder -2.0 × 170 in the left eye. Well-positioned posterior chamber IOL in both eyes and corneal opacities in the right eye, possibly associated with previous recurrent epithelial defects and stromal punctures, were noted.

Preoperative corneal topographic maps generated with the ORBscan II showed regular astigmatism in the right eye (Fig. 2A). Postoperative corneal topography performed 2 years later showed no remarkable changes in comparison with the earlier maps (Fig. 2B). Surgically induced astigmatism of the cornea was 0.2 diopter × 7 in the right eye.

We performed preoperative higher-order aberration analysis because of the low BCVA and slit-lamp findings. To evaluate higher-order aberrations, we initially performed wavefront analysis with a Hartmann-Shack aberrometer (WaveScan; Visx, Santa Clara, CA), but the process was halted because of errors. Thus, examinations with a Tracey aberrometer were performed for further examination. In the preoperative analysis, the right and left eyes showed predominance of fourth-order spherical aberrations (C_4^*) in the entire eye and internal optics, with no remarkable spherical aberration in the corneas (Table). Postoperative higher-order aberrations showed a marked decrease in spherical aberrations originating from the internal optics, possibly as a result of the elimination of anterior lenticonus (Table). Preoperative three-dimensional extraction maps obtained with the Tracey aberrometer also showed a
dominant spherical aberration that mainly originated from the internal optics (Fig. 3A). This markedly decreased after clear lens phacoemulsification with IOL implantation (Fig. 3B). The left eye showed similar changes in spherical aberration (Fig. 4). Preoperative and postoperative root mean squares of the higher-order aberrations are summarized in the table.

After capsulorrhexis for clear lens phacoemulsif-
cination of both eyes, the acquired anterior lens capsules were examined with transmission electron microscopy. The thicknesses of the anterior lens capsules varied from 4.0 to 8.5 µm, thinnest in the center and thickest at the periphery (Fig. 5). The thickness of the lens capsule was decreased in the central and peripheral portions compared with the normal reference range for human anterior lens capsule thickness, 11 to 15 µm. The central portions of the anterior capsule showed multiple dehiscences, especially in the inner two-thirds. The dehiscences were particularly obvious in the central portion of the anterior capsules, but they were also observed in the peripheral portions. Most dehiscences were filled with fibrillar materials and vacuoles (Fig. 5).

**DISCUSSION**

Alport syndrome was first described in 1927 by Alport. The prevalence is 1:5,000 in a normal population. Distribution is equal in males and females, although males are more severely affected. Renal manifestations are noted in childhood, with proteinuria, hematuria, or glomerulonephritis, and usually progress to end-stage renal disease or death in male patients. Life expectancy in patients with Alport syndrome has been improved because of the advent of hemodialysis and renal transplantation. In addition to renal problems, bilateral, symmetrical, and progressive hearing deficiency occurs. The hearing impairment is characterized by reduced sensitivity to high tones in parallel with the de-
development of kidney dysfunction, and it may progress to severe deafness. Findings on auditory tests are consistent with a cochlear lesion. Patients have renal failure and sensorineural hearing loss by 20 years of age.

The diagnosis of Alport syndrome is initially based on clinical and morphologic criteria. According to Flinter et al., it can be diagnosed when at least three of the following criteria are present: a family history of hematuria, with or without progression to end-stage renal disease; progressive sensorineural hearing loss; characteristic ocular changes, such as anterior lenticonus or maculopathy; and ultrastructural abnormalities, including thickening and fragmentation of the glomerular basement membrane. Finally, identification of the mutation confirms the diagnosis. However, this molecular diagnostic gold standard test is limited practically for many reasons, including its high cost, time-consuming nature, and reduced sensitivity.

Ocular changes in Alport syndrome were first reported by Sohar. In Govan's study, the most common ocular defect was dot-and-fleck retinopathy of the macula or midperiphery, which occurred in approximately 87.5% of patients. A retinal lesion is often present at the onset of renal failure, but signs of anterior lenticonus usually appear during the second or third decade. The etiology of Alport syndrome is unknown, but it appears to be related to a widespread disorder of basement membrane collagen. In Alport syndrome, the main problem is defective synthesis of type IV collagen, which is a major structural component of the basement membrane. In the basement membrane, type IV collagen forms mesh structures that function as hinges. In patients with Alport syndrome, because of abnormalities in type IV collagen resulting in a frame structure without hinges, the basement membrane becomes thin and fragile and eventually mechanical damage occurs secondary to accommodation.

The Tracey wavefront aberrometer is unique among automated wavefront measurement devices in that it measures one point at a time, albeit extremely rapidly, with infrared lasers. All measurements are obtained within 15 msec, making it highly unlikely that eye movement could affect the accuracy of measurement. Separate and sequential data capture means that there is no confusion in the analysis between the location of a point in the entrance pupil and the location where that point is observed on the retina. Therefore, highly aberrant eyes are measured easily and accurately with ray tracing technology without the crossover effects that occasionally exist with Hartmann-Shack aberrometry.

This advantage was reported by Moreno-Barriuso and Navarro, who compared laser ray tracing and Hartmann-Shack wavefront sensor methods in artificial and human eyes. They found that the results were similar between both devices in eyes with low amounts of higher-order aberrations. However, for eyes with root mean squares wavefront errors of greater than 2 µm and asymmetrical aberrations, a full measurement could be obtained with laser ray tracing but not with the Hartmann-Shack sensor because of distortion of the array of image spots.

By integrating wavefront aberrometry with corneal topography, the iTrace (Tracey Technologies) combination of ray tracing aberrometry and corneal topography provides an analysis that subtracts corneal from total aberrations to isolate the internal optical aberrations of the eye. Thus, using the Tracey device, we can easily determine whether the main source of irregular astigmatism is the corneal surface or the internal optics.

To the best of our knowledge, this is the first description of anterior lenticonus in Alport syndrome using the Tracey wavefront aberrometer. Previous reports have also shown that the irregular astigmatism in refraction in anterior lenticonus was lenticular in origin with Hartmann-Shack devices. However, Tracey aberrometry may provide more reliable results than Hartmann-Shack aberrometry because of the absence of crossover effects, especially in patients with large amounts of higher-order aberrations, such as patients with anterior lenticonus.

In eyes with anterior lenticonus, the increase in negative spherical aberration is induced by the relatively symmetrical protrusion of the anterior lens surface. As the center of the anterior lens surface protrudes, the central curvature steepens and the peripheral curvature flattens. Our results clearly showed a dominant feature of spherical aberration in lenticular irregular astigmatism, which was consistent with the nature of anterior lenticonus. To identify the source of the irregular astigmatism, it is important to separate irregular astigmatism of the cornea from that of the lens. The root mean squares values of spherical aberration for entire eyes tend to be smaller than those for the internal optics because of compensation for the positive spherical aberration in the cornea. In addition, our data showed increased features in third-order coma and trefoil aber-
rations in the internal optics of both eyes. These results may be caused by either the difference between the apex of the anterior lenticonus and the visual axis or the asymmetrical portion in the protrusion of the anterior lenticonus.

Junk et al.\textsuperscript{10} reported ultrastructural findings in patients with Alport syndrome, including thinning of the central parts of the anterior lens capsule and multiple dehiscences with filamentous connective bridges and vacuolar spaces. Their findings showed that the capsular thickness of anterior lenticonus varied from 5 to 12 µm. Our specimens showed similar findings. The capsular thicknesses of our patient varied from 4.0 to 8.5 µm, with the thinnest diameter in the center and the thickest at the periphery of the capsule. Marked dehiscences in the central portion were also found and may be the result of the stress of accommodation in the area where movement displacement is greatest.

The Tracey wavefront aberrometer is a reliable and effective tool for evaluation of anterior lenticonus in Alport syndrome. Furthermore, ultrastructural changes in the anterior lens could be an important clue in confirming the diagnosis of Alport syndrome.

REFERENCES