Optical Cross-sectional Imaging of the Macula With the Retinal Thickness Analyzer in X-linked Retinoschisis

Angelo P. Tanna, MD; Sanjay Asrani, MD; Ran Zeimer, PhD; Shazhou Zou, MS; Morton F. Goldberg, MD

Objective: To assess the morphologic characteristics of the foveal abnormality in juvenile X-linked retinoschisis using the scanning retinal thickness analyzer (RTA). This characteristic foveal abnormality is present in 83% to 100% of patients with X-linked retinoschisis and has not been demonstrated histopathologically.

Methods: The RTA is a noncontact imaging device. The RTA scans an obliquely oriented slit laser beam across the macula to obtain a series of optical cross sections, which are digitized.

Participants: The RTA was used to examine 7 eyes of 5 patients with X-linked retinoschisis.

Results: The RTA demonstrated foveal schisis in all eyes examined. In 2 eyes of 2 patients, a single schisis cavity, with an inner leaf in a dome-shaped configuration, was present. In 4 eyes of 3 patients, a single schisis cavity containing fine strands was present. Some of these strands partially, and others completely, bridged the cavity. In 1 eye of 1 patient, 2 separate schisis cavities with bridging strands were present in the fovea.

Conclusions: Scanning RTA is a noninvasive imaging modality capable of producing optical cross sections that demonstrate the extent and structural details of the foveal schisis in X-linked retinoschisis. Scanning RTA seems to be effective in the detection, characterization, and quantification of foveal schisis.


JEUNILE X-LINKED retinoschisis (XLRS) is a bilateral hereditary vitreoretinal dystrophy thought to be the result of a primary abnormality of Müller cells.1,2 Using link-age analysis, the gene has been mapped to band Xp22.2, allowing carrier detection.3,4 The disorder is characterized by foveal schisis that has been reported to be present in infancy.5,6 Although easily missed with ophthalmoscopy, especially in an uncooperative child, the characteristic bilateral foveal schisis is present in 83% to 100% of patients with XLRS and is the only abnormality detected with ophthalmoscopy in about 29% to 50% of patients.5,7 In addition, approximately 50% to 71% of patients exhibit peripheral retinoschisis.5,7 Patients typically demonstrate decreased visual acuity, but strabismus or nystagmus also may be early presenting signs. The disease is progressive, and the course may be complicated by vitreous hemorrhage or full-thickness retinal detachment.5,7

Haas,8 in 1898, was the first to describe the ophthalmoscopic details of the foveal abnormality. Results of biomicroscopic examination of the fovea typically reveal an “optically empty zone, delimited by two retinal layers of which the more superficial one is very thin and has a typical spoke-like radial plication pattern.”5 Microcysts and cystoid structures in the foveal center have been described as well.5,9 The morphologic features of the foveal schisis evolve over time, with collapse of the schisis cavity, which may disappear completely in older patients.5,7,9

Scanning retinal thickness analysis (RTA) (Talia Technology Ltd, Mevaseret Zion, Israel) is a new technique to rapidly scan and obtain multiple high-resolution optical cross sections of the retina at the posterior pole.10 Its use in detecting abnormalities of retinal thickness at the macula is being actively investigated in the evaluation of macular edema,11-13 macular holes,14 and other retinal disorders.15 We examined 7 eyes of 5 patients with XLRS and demonstrated details of the foveal abnormality using this new imaging modality.

RESULTS

The history and clinical and RTA findings are summarized in the Table.
PATIENTS, MATERIALS, AND METHODS

SCANNING RTA

The principle of the RTA is based on projecting a thin green helium-neon laser slit beam obliquely onto the retina and viewing the image at an angle in a manner similar to slitlamp biomicroscopy. The reflected images of the intersections of the laser slit beam with the retina, described in this article as an optical cross section of the retina, are recorded by a video camera and digitized. The separation between the reflections and the scatter from the vitreoretinal interface and from the chorioretal interface provides a measure of the retinal thickness.

The commercial scanning RTA used in this study is a further technical development of this method, which provides multiple optical cross sections in 1 brief scan. More specifically, a 2-mm-long laser slit beam is projected vertically onto the retina and scanned. In a total of 200 milliseconds, 10 scans, each 200 µm apart, are obtained, thus covering a 2 × 2-mm area of the macula.

Before measurement, the pupil is dilated to at least 5 mm. An incandescent lamp illuminates a conjugate focal plane of the fundus. At this plane, a screen with fixation targets is placed and then viewed by the patient. The illumination is also used to image the fundus on a video camera. The fundus image is viewed on a screen during alignment and recorded after each scan. This allows the operator to verify the fixation, observe the location of pathologic disorders, help guide patients who cannot fixate because of low vision, and document the location of each scan on the fundus. The technology to record the fundus image and document the precise location of the scanned area was unavailable when patient 2 was studied.

When precise measurement values are important, the axial length and the refractive error are measured. With these parameters and a table derived from optical principles, the exact magnification and thickness conversion are obtained. Because a high degree of precision would not add to the findings of this article, we preferred to limit the procedures performed on these young patients to RTA scans.

PATIENTS

This study was approved by the Joint Commission of Clinical Investigation of The Johns Hopkins Medical Institutions, Baltimore, Md. The patients were recruited from various clinical services of The Wilmer Ophthalmological Institute, Baltimore. Informed consent was obtained from the parents of each patient before examination with the RTA. Patients underwent a complete ophthalmologic examination, including slitlamp biomicroscopy with a fundus contact lens (except patient 4) and fundus photography, before referral for RTA imaging.

PATIENT 1

The patient was initially diagnosed as having XLRS at 5 years of age, based on the presence of foveal schisis, and was first examined at The Wilmer Ophthalmological Institute at 13 years of age. At that time, visual acuity was 20/60 OD and 20/100 OS. Results of ophthalmoscopic examination disclosed foveal schisis with a typical stellate pattern emanating from the foveal center in both eyes. Results of examination of the left eye also revealed a large schisis cavity extending from just inferior to the inferotemporal arcade to the midperiphery, with a surrounding zone of pigment migration. There was no family history of XLRS; however, he had no brothers or maternal uncles.

The right eye was imaged with the RTA at age 13 years, which disclosed a well-demarcated schisis cavity that was delimited by 2 retinal layers in the region of the fovea (Figure 1). A single schisis cavity was present, but its nasal extent was not completely imaged because it extended outside the 2000-µm horizontal excursion of the RTA. The inner leaf of the schisis cavity had a shallow domelike configuration. The retinal pigment epithelium–choroid layer was flat. Although retinoschisis was detected with slitlamp biomicroscopy, the dimensions of the schisis cavity were only quantifiable with the RTA. The schisis cavity measured up to 240 µm anteroposteriorly and up to 1470 µm vertically. The left eye was not studied with the RTA.

PATIENT 2

The patient was diagnosed as having XLRS at age 3 years, when he was seen with nystagmus. There was a family history of what was originally and erroneously thought to be X-linked retinitis pigmentosa. At age 9 years, the best-corrected visual acuity was 20/80 OD and 20/70 OS. Horizontal jerk nystagmus was present. Results of ophthalmoscopic examination of both eyes revealed the characteristic foveal schisis with a spokelike pattern of cysts with septa. It could not be determined if the septa completely bridged the schisis cavity. Sheathing of the peripapillary vessels, large peripheral schisis cavities with retinal vessels bridging holes in the inner leaves, and diffuse vitreous “veils” were present.

Scanning RTA images of the right eye revealed 2 distinct areas of schisis in the region of the fovea (Figure 2). The height of the more temporally situated cavity varied in a pattern suggesting a rippled appearance of the inner leaf. In all the sections that revealed schisis, there were fine strands bridging the 2 leaves of the schisis cavity—some partially, others completely (Figure 2 and Figure 3). The larger schisis cavity measured up to 230 µm anteroposteriorly and 1800 µm vertically. The temporal extent of the more temporally situated schisis cavity and the nasal extent of the more nasally situated schisis cavity were not included in the study because they extended outside the 2000-µm horizontal scanning area. In the left eye, only 1 schisis cavity was present in the fovea (Figure 4). The nasal and temporal extents of the schisis cavity were not included in the study because they extended outside the 2000-µm horizontal scanning area. The schisis cavity measured up to 240 µm anteroposteriorly and 1600 µm vertically.

PATIENT 3

The patient was diagnosed as having XLRS at 4 years of age, when he was seen with esotropia. At that time, the
best-corrected visual acuity was 20/30 OD and 20/60 OS. There was a family history of blindness in a maternal uncle and 2 maternal male cousins. Ophthalmoscopic examination revealed foveal schisis with the typical radial pattern emanating from the foveal center in both eyes. In the left eye, there was an extensive area of peripheral schisis as well as a tractional retinal detachment inferior to the macula. The patient underwent a scleral buckling procedure but had a persistent tractional retinal detachment involving the macula. He subsequently has experienced 4 episodes of vitreous hemorrhage in the left eye.

At age 9 years, the patient complained of acute loss of vision in the left eye after mild trauma. Visual acuity at that time was 20/40 OD and counting fingers OS. Results of slit-lamp biomicroscopy of the right eye revealed hyperpigmentation in the foveal region at the level of retinal pigment epithelium and a subtle radial striated pattern with barely detectable retinoschisis in the right eye at the time of imaging with the retinal thickness analyzer.

<table>
<thead>
<tr>
<th>Patient No./Age at Diagnosis, y</th>
<th>Family History</th>
<th>Visual Acuity at Time of Imaging*</th>
<th>Macular Findings</th>
<th>Peripheral Retinoschisis</th>
<th>Vitreous Findings</th>
<th>Other Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/5</td>
<td>No</td>
<td>20/60 OD and 20/100 OS</td>
<td>Foveal schisis with a typical stellate pattern OU</td>
<td>Present OS</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>2/3</td>
<td>Yes</td>
<td>20/80 OD and 20/70 OS</td>
<td>Foveal schisis with a spokelike pattern of cysts with septae OU</td>
<td>Present OU</td>
<td>Vitreous “veils” OU</td>
<td>Nystagmus</td>
</tr>
<tr>
<td>3/4</td>
<td>Yes</td>
<td>20/40 OD and CF OS</td>
<td>Foveal schisis with a typical radial pattern emanating from the foveal center OU at the time of diagnosis; hyperpigmentation in the foveal region at the level of retinal pigment epithelium and a subtle radial striated pattern with barely detectable retinoschisis in the right eye at the time of imaging with the retinal thickness analyzer</td>
<td>Present OD</td>
<td>Vitreous hemorrhage OS</td>
<td>Esotropia</td>
</tr>
<tr>
<td>4/2</td>
<td>No</td>
<td>CF OD and 20/25 (Allen pictures) OS</td>
<td>Retinal fold through the center of the macula OD; radiating folds in the foveal region OS</td>
<td>Present OU</td>
<td>Vitreous “veils” OD; Sclerotic avulsed retinal vessel in vitreous OS</td>
<td>Electroretinographic reduction in B-wave amplitude with relative enhancement of A wave</td>
</tr>
<tr>
<td>5/5</td>
<td>Yes</td>
<td>20/80 OU</td>
<td>Radially oriented foveal cysts with septae OU</td>
<td>Present OS</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

*CF indicates counting fingers.
erate elevation of the inner leaf (Figure 5). The nasal extent of the schisis cavity is not included in the imaging study because it extended outside the 2000-µm horizontal scanning area. Fine strands spanned the schisis cavity, bridging the inner and outer leaves. In the optical section in which the area of the schisis cavity is the largest, the inner leaf of the schisis cavity was extremely thin (Figure 5, arrowheads). The schisis cavity measured up to 160 µm anteroposteriorly and 1120 µm vertically.

PATIENT 4

The patient was first seen at age 2 years, when the parents noted esotropia. There was no family history of XLRS or other ocular disease. The patient objected to occlusion of the left eye and maintained steady, central fixation with the left eye. There was a 30-PD right esotropia. Results of examination of the right eye revealed vitreous “veils” that were most notable superiorly. A tubular retinal fold extended from the margin of the optic nerve head inferotemporally, through the fovea, to the equator, with hyperpigmentation along the fold. Results of examination of the left eye revealed the characteristic radiating folds in the foveal region, compatible with the diagnosis of XLRS. A sclerotic avulsed retinal vessel was present in the vitreous temporal to the macula. An electroretinogram recorded from the right eye, while the patient was under general anesthesia, demonstrated a reduction in the B-wave amplitude with relative enhancement of the A wave, consistent with the diagnosis of XLRS.1

The patient was most recently examined at age 6 years, when the best-corrected visual acuity was count-
ing fingers OD and 20/25 (Allen pictures) OS. Results of noncontact slitlamp biomicroscopy of the fundus disclosed no change in the retinal fold through the center of the right macula and no change in radial folds of the left fovea (Figure 6). Results of indirect ophthalmoscopy disclosed peripheral retinoschisis in both eyes.

Retinal thickness analysis of the left eye was performed at 6 years of age (Figure 6). A single, well-demarcated, dome-shaped schisis cavity with bridging strands was present in the fovea. The schisis cavity measured up to 190 µm anteroposteriorly, 1300 µm vertically, and approximately 1800 µm horizontally. The right eye was not imaged with the RTA because of the presence of the retinal fold through the central macula.

PATIENT 5

The patient was diagnosed as having XLRS at 5 years of age, based on the ophthalmoscopic appearance, when he was first evaluated after failing a school vision screening examination. There was a family history of a retinal disease that affected several male children of a maternal grand aunt. He was first seen at The Wilmer Ophthalmological Institute at 10 years of age, when results of examination disclosed vision of 20/80 OU, radially oriented foveal cysts with septa in both eyes, and peripheral retinoschisis with large inner leaf holes in the left eye. The findings remained unchanged during the next 2 years.

Retinal thickness analysis of the right eye (Figure 7), performed when the patient was 12 years old, revealed a dome-shaped schisis cavity with a thin inner leaf and fine bridging strands. The schisis cavity measured up to 270 µm anteroposteriorly, 1200 µm vertically, and approximately 1600 µm horizontally. The left eye (Figure 8), a markedly shallow schisis cavity with a thin inner leaf, was present. The schisis cavity measured up to 120 µm anteroposteriorly and 960 µm vertically. The temporal extent of the left schisis cavity was not included in the study because it extended outside the 2000-µm horizontal excursion of the scan. Although septa were detected with slitlamp biomicroscopy, the fact that they entirely bridged the schisis cavity and the dimensions of the schisis cavity were only determined with the RTA.

COMMENT

Foveal retinoschisis is pathognomonic of XLRS and is critically important in establishing the diagnosis, especially in patients in whom the diagnosis is made anew, without a previous family history of the disease, and in whom there are no other visible retinal abnormalities. There are scant data in the literature regarding the histopathologic findings in XLRS. Of the published re-
ports, only 2 contain a description of the changes at the macula, and none reports on the foveal retinoschisis. Manschot reported the histopathologic findings in the macular region in a 60-year-old man with XLRs whose eyes were enucleated 4 hours after death. There was a folded, thickened internal limiting membrane; degeneration of the nerve fiber layer; and atrophy and proliferation of the retinal pigment epithelium.

In patients with XLRs, a consistent histopathologic finding has been retinoschisis at the level of the inner retina, specifically at the inner limiting membrane, nerve fiber layer, or ganglion cell layer. In all 5 of our patients, optical cross-sectional images of the macula obtained with the RTA clearly demonstrated retinoschisis in the region of the fovea; however, it is not possible to determine the histological level of the separation within the retina using this technique. In patient 3 and in the left eye of patient 5, for example, there is a definite separation within the retina; however, the inner leaf is only slightly to moderately elevated compared with the schisis cavities in other patients. This type of morphologic condition may represent a more advanced stage of the foveal abnormality wherein the typical schisis cavity has begun to collapse. As patients with XLRs get older, the biomicroscopic appearance of the fovea changes until finally only nonspecific pigmentary changes, without ophthalmoscopically apparent retinoschisis or the radial pattern, are present. There may be a continuum between the classic morphologic condition and the disappearance of retinoschisis.

Yanoff et al reported the pathologic findings in a 4-year-old boy with XLRs who underwent enucleation on the suspicion of retinoblastoma. They found peripheral retinoschisis at the level of the nerve fiber layer, with inner wall of the schisis cavity consisting of internal limiting membrane, inner portions of Muller cells, blood vessels, and remnants of nerve fiber layer. They also found occasional septa or strands in areas of peripheral schisis composed of compressed and fused remnants of axons and Muller cells bridging the 2 leaves of the schisis cavity. Our findings in patients 2 through 5 also revealed strands bridging the macular schisis cavity and may represent similar structures within the macula.

The morphologic characteristics of some macular lesions that can be identified by the experienced examiner during slitlamp biomicroscopy are often inadequately recorded with fundus photography, limiting the extent to which photographic documentation can be used to demonstrate the pathologic findings or monitor the course of disease. The RTA operates on the principle of laser biomicroscopy and provides a degree of sensitivity that allows optical cross-sectional imaging of the retina at the posterior pole and can identify abnormalities that may be difficult to detect with conventional biomicroscopy alone.

The foveal schisis that is pathognomonic of XLRs is often a subtle ophthalmoscopic finding that can be difficult to detect and easily overlooked, especially in an uncooperative child. In all 5 patients, the foveal schisis was more readily detected with the RTA than with conventional biomicroscopy or ophthalmoscopy. In addition, we demonstrated that the morphologic characteristics of the schisis cavity can be evaluated in detail and quantified. Future studies should be directed at monitoring patients serially to follow the progression of the foveal schisis over time. Although this may have limited therapeutic use at present, it may serve valuable diagnostic and prognostic roles; for example, in correlating foveal morphologic findings with visual function.

In summary, the RTA allows noninvasive, cross-sectional imaging of the retina at the posterior pole, readily demonstrating the foveal abnormality in XLRs, a finding previously not described in histopathologic studies. This technique may be valuable in establishing the diagnosis of XLRs in clinical situations in which ophthalmoscopy or biomicroscopy is inadequate. In addition, the RTA may be useful for serial documentation of the foveal abnormalities in patients with XLRs and other diseases in which retinal thickness is altered in the macular region.

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Reprints: Ran Zeimer, PhD, Ophthalmic Physics Laboratory, Wilmer Ophthalmological Institute, The Johns Hopkins University School of Medicine, 600 N Wolfe St, Wilmer Woods Bldg 355, Baltimore, MD 21287-9131.