Objective

To investigate the retinal microstructure and lamination of patients affected with X-linked retinoschisis (XLRS) using high resolution imaging modalities. FD-OCT imaging was done using RTVue (Optovue Inc,Fremont,California,USA) version 4 system.

Materials and Methods

Data was collected from 20 eyes of 10 patients diagnosed to have XLRS who attended our outpatient department between October 2008 and June 2010. A comprehensive eye evaluation included best-corrected distant visual acuity (using Snellen’s Chart), anterior segment examination, color vision testing (using Ishiara test plates with a standard illumination), full-field electroretinography (ERG) (using the International Society for Clinical Electrophysiology of Vision standard)[4] and a dilated fundus examination.

High-resolution retinal image acquisition was performed using a high-speed, high-resolution FD-OCT RTVue Scanner version 4 (26,000 A-scan/second, Frame Rate: 256 to 4096 A-scan/Frame Depth Resolution (in tissue) : 5.0µm and Transverse Resolution: 15µm).

Horizontal scans of 6 mm were obtained through the macular area. Retinal layers were identified on the basis of previously published data[5] and compared with control data as shown in Figure 1. Control data was obtained by scanning 10 age matched controls with RTVue scanner. FD-OCT Retinal structure analysis was performed on at least 3 macular scans through the fovea of each eye. Each scan was analyzed for schisis location within the foveal and parafoveal area and the integrity of the photoreceptor inner and outer segment layers. This study was designed as a retrospective cross-sectional observational case series.

Results

Twenty eyes of 10 male patients diagnosed to have XLRS underwent testing. Age of the patients ranged from 11 years to 72 years. Visual acuity ranged from counting fingers 2 meters to 6/36. Two patients had immature cataract in both the eyes (patients 3 and 4)(table 1). Color vision defects were detected in 2 patients (patients 3 and 6)(table 1). The low visual acuity precluded color vision testing in 6 patients (patients 4, 6, 7, 8, 9 and 10)(table 1). Fundus changes included macular schisis (cartwheel appearance), blunted macular reflex and atrophic macular changes. ERG responses showed an abnormal b to a waves in all patients.

Introduction:

Retinoschisis or splitting of retina has been reported as early as 1898[6]. X-linked retinoschisis (XLRS) is caused by mutations in the XLRS1 gene (OMIM 312700) on Xp22 encoding retinoschisin,[7] which is primarily expressed in photoreceptor and bipolar cells.[8] Morphological classification of this retinal abnormality using Fourier-domain OCT is not well established. The purpose of the present study using a high speed, high-resolution Fourier-domain OCT (FD-OCT) system was to provide higher resolution characterization of the retinal layer abnormalities associated with XLRS.
Analysis of FD-OCT scans showed foveal schisis with three typical morphological appearances. The first type was bullous foveal contour (BFS) [figure 2] where the fovea appeared convex and schisis cavities involved all layers of the retina. This configuration was noted in 6 patients (symmetric foveal morphology in 3 patients and asymmetric foveal morphology in 3 patients) (table 1). Average central foveal thickness in this group (9 eyes) was 346 microns. The second type was with a relatively normal foveal contour (NFC) [figure 3] where schisis cavities appeared to relatively spare the ganglion cell layer. This appearance was seen in 2 patients (1 patient with symmetric foveal morphology and 1 patient with asymmetric foveal morphology) (table 1). Average central foveal thickness in this group (4 eyes) was 156 microns. In the third type, fovea was flat and thinned out with sieve like appearance of all the layers (Flat foveal contour (FFC)) [figure 4]. Analysis of OCT images could not delineate the different retinal layers in this subset of patients. This pattern was noted in 4 patients (3 patients with symmetric foveal morphology and 1 patient with asymmetric foveal morphology) (table 1). Average central foveal thickness in this group (7 eyes) was 126 microns.

The retinal outer segment layer (OSL) and inner segment layer (ISL) could be clearly differentiated in 3 patients (patients 1, 3, and 6) (table 1). In these patients ISL OSL junctions appeared morphologically disrupted. The remaining 7 patients showed gross disruption of the outer layers. No patient had peripheral retinal schisis.

<table>
<thead>
<tr>
<th>Patient No./Age</th>
<th>OD/OS V, Snellen</th>
<th>Color defect</th>
<th>Fundus</th>
<th>Foveal schisis RE/LE</th>
<th>Layers involved</th>
<th>Foveal Parafoveal</th>
<th>Foveal OSL/ISL</th>
<th>CFT (microns) RE,LE</th>
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</thead>
<tbody>
<tr>
<td>1/23 years</td>
<td>6/60,6/36</td>
<td>N</td>
<td>Macular schisis</td>
<td>B/B</td>
<td>IPL-ONL</td>
<td>ONL-GCL</td>
<td>Irregular</td>
<td>352,358</td>
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<td>2/11 years</td>
<td>6/36,6/36</td>
<td>N</td>
<td>Macular schisis</td>
<td>B/B</td>
<td>IPL-ONL</td>
<td>ONL-GCL</td>
<td>NA</td>
<td>342,356</td>
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<tr>
<td>3/54 years</td>
<td>6/36,6/60</td>
<td>present</td>
<td>Macular schisis</td>
<td>N/N</td>
<td>IPL-ONL</td>
<td>IPL-ONL</td>
<td>Irregular</td>
<td>162,151</td>
</tr>
<tr>
<td>4/72 years</td>
<td>CF2mt,CF2mt</td>
<td>NA</td>
<td>Atrophic</td>
<td>F/F</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>128,120</td>
</tr>
<tr>
<td>5/22 years</td>
<td>6/36,CF2mt</td>
<td>N*</td>
<td>Macular schisis</td>
<td>B/N</td>
<td>IPL-ONL</td>
<td>ONL-GCL, IPL-ONL</td>
<td>NA</td>
<td>350,160</td>
</tr>
<tr>
<td>6/12 years</td>
<td>6/60,6/36</td>
<td>present</td>
<td>Macular schisis</td>
<td>B/B</td>
<td>IPL-ONL</td>
<td>ONL-GCL</td>
<td>Irregular</td>
<td>332,336</td>
</tr>
<tr>
<td>7/28 years</td>
<td>6/60,CF3mt</td>
<td>N*</td>
<td>Macular schisis</td>
<td>B/N</td>
<td>IPL-ONL</td>
<td>ONL-GCL, IPL-ONL</td>
<td>NA</td>
<td>346,150</td>
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<tr>
<td>8/35 years</td>
<td>CF4mt,CF5mt</td>
<td>NA</td>
<td>Blunt reflex</td>
<td>F/F</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>132,124</td>
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<tr>
<td>9/21 years</td>
<td>6/36,CF2mt</td>
<td>N*</td>
<td>Macular schisis</td>
<td>B/F</td>
<td>IPL-ONL,NA</td>
<td>ONL-GCL, NA</td>
<td>NA</td>
<td>340,126</td>
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<tr>
<td>10/46 years</td>
<td>CF2mt,CF3mt</td>
<td>NA</td>
<td>Atrophic</td>
<td>F/A</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>128,130</td>
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</tbody>
</table>

N*=fellow eye color vision could not be tested, N= normal, mt=meters, OPL=Outer nuclear layer, IPL=Inner plexiform layer, GCL=Ganglion cell layer, NA=Not applicable, CFT=Central foveal thickness, BFS=Bullous foveal contour, F=Flat foveal contour, N=Normal foveal contour
Discussion

X-linked juvenile retinoschisis (XLRS) is characterized by symmetric bilateral macular involvement with onset in the first decade of life\[^8\], in some cases as early as age three months. Males are usually affected by this disease. Splitting of the retina occurs in the nerve fibre layer and traditionally it is thought that schisis involves the inner layers of the retina sparing the outer layers.

In vivo characterization of retinal structures in XLRS was performed using high-speed, high-resolution RTVue FD-OCT, to our knowledge for the first time. We were able to demonstrate abnormalities in all layers of the retina and describe three distinct FD-OCT morphological patterns in this disease.

In our series age of patients ranged from 11 years to 72 years. All patients below 30 years had a classic cart wheel pattern of macular schisis on fundus examination. Two out of three patients above 40 years showed a dry and atrophic macula, and on OCT scanning demonstrated a flat foveal contour (FFC).

Visual acuity in our group of patients ranged from CF2 meters to 6/36. Two patients (aged 54 years and 72 years) had immature cataract but not significant enough to prevent OCT evaluation of the macula. However, the effect of cataract could have had on visual acuity on these patients could not be clearly ascertained. In our study patients whose fundus examination showed a clinically atrophic macula and on OCT scanning revealed a flat foveal contour demonstrated a flat foveal contour (FFC).

Colour vision defects in XLRS is found to be more severe in older patients than in younger ones\[^6\]. Colour vision abnormalities were noted only in 2 patients (patient 3 aged 12 years and patient 6 aged 54 years) in our series. Elise et al\[^1\] in their study of 6 patients with XLRS detected colour vision abnormalities in 3 patients. One confounding factor in our study was that low visual acuity in many patients precluded testing for color vision abnormalities which otherwise would have been present (table 1).

Different morphological classification schemes for XLRS exists based on both clinical and OCT findings\[^11\]. This includes 6 cystic subtypes and the atrophic type\[^10\]. In this present study FD-OCT scanning revealed 3 distinct types of central foveal patterns which we classified as, Bullous foveal contour (BFC), Normal foveal contour (NFC) and Flat foveal contour (FFC).

In the Bullous foveal contour (BFC) pattern the fovea appeared convex and schisis cavities involved all layers of the retina. In this group we could demonstrate schisis cavities from inner plexiform layer to outer nuclear layer at the fovea (as inner layers are thinned out at the fovea) and outer nuclear layer to ganglion cell layer at the parafovea. This configuration was noted in 9 out of 20 eyes in our study and clinically correlated with a fundus appearance of a typical macular schisis. Patients in this group belonged to a younger age group (<30 years) and had better visual acuities in comparison to other groups (visual acuity of 6/60 or better).

In the Normal foveal contour (NFC) subtype the schisis cavities appeared to relatively spare the ganglion cell layer (inner plexiform to outer nuclear layers involved). This morphology also corresponded with a fundus appearance of typical macular schisis. We could not find a relationship between this OCT morphology and age of the patient or his visual acuity. To our knowledge this OCT appearance has never been described before in XLRS. This could be an intermediate stage in the flattening of schisis cavities that is known to occur with advancing age\[^10\].

In the Flat foveal contour pattern (FFC) analysis of OCT images could not delineate the different retinal layers and schisis cavities could be seen throughout the retina.
pattern most likely represents thinning and atrophy of the fovea that occurs with advancing disease and was associated with poor visual acuity. B. Lesch et al. in their study of 72 eyes with XLRS noted a conversion of cystic form of the disease to retinal atrophy after the age of 26 years. We also noted similar results in our study (3 out of 4 patients with this pattern being over 30 years).

Unlike other retinal dystrophies central fovea is found to be abnormally thicker in XLRS due to large cystic cavities involving the fovea. In our series this was found to vary with varying morphological patterns of the disease. Central fovea was found to be abnormally thick in the bullous pattern (BFC) and abnormally thin in the atrophic subtype (FFC). We have hypothesized that that the three subtypes that we have described in this study represents the varying spectrum of disease progression. It maybe that the early form of the disease may represent a bullous foveal contour which on progression may flatten out to a relatively normal foveal contour and in the end resulting in an atrophic thin fovea (FFC).

FD-OCT machines are superior to time domain OCT machines in tissue delineation and identification of retinal microstructures. Inner segment (IS) – Outer segment (OS) junction abnormalities represent photoreceptor layer damage and could be detected in 3 out of 10 patients in our study. Elise et al in their study of 6 cases of XLRS demonstrated IS-OS junction irregularities in 4 patients using FD-OCT scanning. Even with FD-OCT, detection of these abnormalities is difficult, especially with schisis cavities obscuring the retinal layers.

Conclusion

Retinal dystrophy in XLRS is reflected by morphological changes within the inner and outer retinal layers. The different morphological patterns as detected by FD-OCT imaging may help to identify disease progression and severity.

References

1. Christina Gerth, MD; Robert J. Zawadzki, PhD; John S. Werner, PhD; Elise He´on, MD.; Retinal Morphological Changes of Patients With X-linked Retinoschisis Evaluated by Fourier-Domain Optical Coherence Tomography: Arch Ophthalmol. 2008;126(6):807-811.
8. Paul A Sieving MD; X-linked juvenile retinoschisis Gene reviews:NCBI.