

17 **Abstract**

18 **Purpose**

19 To evaluate the presence of retinal nerve fiber layer (RNFL) defects in patients with XLRS
20 using high speed, high resolution, Fourier domain OCT (FD-OCT).

21 **Methods**

22 Twenty four patients with XLRS seen by the authors were enrolled in the study. All patients
23 underwent a complete eye examination. FD-OCT was performed using Optovue technology.
24 A quadrant of the RNFL was considered to be thinned if at least 2 of the 4 segments in the
25 quadrant were reduced in thickness.

26 **Results**

27 The average age of the 24 patients in the study was 28.8 years \pm 14.7 years. Thinning of the
28 RNFL in 1 quadrant was seen in 10 patients (41.7%), and thinning in 2 or more quadrants
29 was seen in 8 patients (33.3%). Thinning in the inferior quadrant was most commonly seen
30 and was observed in 12 patients (50%), followed by the temporal quadrant in 8 patients
31 (33.3%), nasal quadrant in 4 patients (16.7%), and the superior quadrant in 4 patients
32 (16.7%).

33 **Conclusions**

34 Among our 24 patients with XLRS, 15 patients (62.5%) showed a thinning of the RNFL in
35 one or more quadrants in at least one eye and 9 patients (37.5%) in both eyes. The use of high
36 speed, high resolution FD-OCT may be useful to determine the presence of possible changes
37 in RNFL thickness in patients with XLRS. Reductions in RNFL thickness in such patients
38 could be relevant in their selection for future therapeutic trials.

39 **Keywords:**

40 X-linked retinoschisis; nerve fiber layer thickness; Fourier-domain OCT

41

42 **Introduction**

43 Juvenile X-linked retinoschisis (XLRS) was described as early as 1898 by Haas¹ and several
44 years later, it was identified by Mann and MacRae² in 1938 to have an X-linked recessive
45 inheritance. It occurs almost exclusively in males and is characterized by a progressive
46 decrease of central visual acuity in the first years of life and the presence of foveal cystic,
47 spoke wheel-like lesions at the macula apparent on fundus examination. A typical feature of
48 this disease is a selective or predominant reduction of the scotopic b-wave amplitude
49 (negative ERG) upon stimulation of the retina with a white-light single flash.³ However,
50 Renner et al, reported that 40% of XLRS patients did not show a negative ERG.³

51 Mutations in the *RS1* gene have been described in patients affected with this disease.⁴ The
52 gene has six exons encoding for the retinoschisin polypeptide of 224 amino acids, which is
53 synthesized in photoreceptor cell inner segments and provides cell adhesion and proper
54 interaction between cells within the inner nuclear layer as well as synaptic connections
55 between bipolar cells and photoreceptors.⁵⁻⁹ The mutant *RS1* gene causes primarily the inner
56 retinal layers to split. Histopathologic examinations suggest that the likely primary lesion in
57 X-linked retinoschisis occurs initially in the innermost portion of Müller cells or at the border
58 of the retinal nerve fiber layer.¹⁰⁻¹²

59 In patients with XLRS, mutations in the *RS1* gene lead to the accumulation of retinoschisin
60 within the inner retina¹³ and the development of cystic-like spaces primarily in the inner
61 nuclear and outer plexiform layers of the retina observed by optical coherence tomography
62 (OCT).¹⁴⁻¹⁶

63 A recent study by Apushkin et al suggested that reduction of visual acuity does not
64 correspond to the size of cystic areas or retinal thickness of the macula as evaluated by time-

65 domain optical coherence tomography (OCT).¹⁷ Gerth et al, using high-resolution OCT,
66 concluded that there is disturbed foveal photoreceptor cell layer integrity in XLRS patients.
67 Retinal layer abnormalities correlated with age but did not appear to correlate with visual
68 acuity loss or genotypic variation.¹⁸

69 The purpose of the current study was to use high speed, high resolution Fourier domain OCT
70 (FD-OCT) to evaluate the presence of any retinal nerve fiber layer (RNFL) defects in patients
71 with XLRS.

72 **Materials and methods**

73 **Participants**

74 The study was conducted in the Department of Ophthalmology at the University of Illinois at
75 Chicago. It followed the tenets of the Declaration of Helsinki and was approved by an
76 institutional review board at the University of Illinois. Twenty four patients (43 eyes) with
77 XLRS were included, and informed consent was obtained on all participants.

78 The diagnosis of XLRS was based on the history of a decrease in central vision within the
79 first decade of life, selective or predominant reduction of the ERG b-wave in light and dark
80 adapted responses and presence of characteristic fundus cystic lesions of the macula.

81 Patients with a diagnosis of XLRS who were seen by the authors (M.G. & G.A.F.) during
82 their routine clinical follow up examinations were included in the present study if they were
83 willing to undergo OCT testing. Additional patients previously seen by one of the authors
84 (G.A.F.) were contacted by telephone and asked to participate in the study based on their
85 prior diagnosis of XLRS.

86 Exclusion criteria included an inability to maintain steady fixation, past history of glaucoma
87 and or increased intraocular pressure of ≥ 21 mmHg, pseudophakic and aphakic patients,
88 posterior uveitis, diabetic retinopathy, optic neuropathies, spherical refraction of more than \pm
89 6 diopters (D) or cylinder refraction of ± 2 D , or any central media opacity sufficient to
90 hinder an OCT examination. No patients with a history of any systemic diseases such as
91 hypertension or diabetes mellitus were included.

92 **Ocular examination**

93 All patients underwent a complete eye examination, including best-corrected visual acuity
94 (BCVA) using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart (The
95 Lighthouse, Long Island City, NY), slit-lamp biomicroscopic examination of the anterior
96 segment, and intraocular pressure (IOP) measurement with Goldmann applanation tonometry.
97 A pachymetry measurement (Nidek Inc., Fremont, CA) was made if the IOP pressure was
98 between 18-20 mmHg on two readings or the optic disc showed any degree of pallor. Both
99 eyes were dilated with 2.5% phenylephrine and 1% tropicamide. Fundus examination was
100 performed using both direct and indirect ophthalmoscopy as well as biomicroscopy with a
101 noncontact 78 D lens and any optic disc pallor was recorded.

102 **Optical coherence tomography (OCT) techniques**

103 OCT was performed using Optovue technology (RTvue version 3.5; Optovue Inc., Fremont,
104 CA). The NMH₄ protocol was used for scan acquisition which consisted of 12 radial line
105 scans, 3.4 mm in length and 6 concentric rings (2.5-4.0mm diameter), all centered on the
106 optic disc. Internal fixation was used for all patients. The total time for a single scan
107 acquisition was 0.39 seconds. Scans were accepted only if they had a signal strength index
108 greater than 35 and were free of artifacts.

109 RNFL thickness was measured automatically by the existing software at a diameter of 3.45
110 mm around the center of the optic disc. The total number of A-scans at that circumference
111 was 9510. RNFL thickness was measured in the superior (46° - 135°), nasal (316° - 45° for the
112 right and 136° - 225° for the left), inferior (226° - 315°), and temporal (136° - 225° for the right
113 and 316° - 45° for the left) quadrants. OCT software automatically measured 4 smaller
114 segments within each quadrant (Figs 1-2). Data thus obtained were compared with the
115 normative database provided with the software, taking the patient age and size of the optic
116 disc into account.

117 RNFL thickness was measured at least 3 times in each eye and data were used only if the
118 scans were reproducible, within either a normal or abnormal range, in at least 2/3 of the scan
119 acquisitions. Also, eyes with scans inconsistent on the first set of 3 OCT RNFL scans were
120 rescanned with another set of 3 scans. We then used the criteria that 2/3 of these scans should
121 be consistent as either normal or abnormal in order to be included in the analysis. In 29 eyes
122 (67.4%) only one set of scans was required, while in 14 eyes (32.6%) two sets of scans were
123 required.

124 One hundred forty three OCT scans were obtained on 43 eyes (1 eye each was tested in 5
125 patients and both eyes were tested in 19 patients). Inner and outer automated machine drawn
126 contour lines which mark the boundary of the nerve fiber layer were examined in each scan
127 and scans with boundary line misplacements leading to distortion of the contour lines were
128 excluded. The contour of the optic nerve head was manually traced using a fundus image
129 generated by the OCT.

130 For detecting changes within the macula in the XLRS patients, we also scanned the macula
131 using both the MM5 and the Radial Lines protocols. The radial scan consisted of twelve 6-

132 mm radial scans at 15° intervals passing through the center of the fovea. All 12 scans were
133 acquired simultaneously and the total time taken for their acquisition was 0.27 seconds. Each
134 radial line consisted of 1024 A-scans.

135 The MM5 scan protocol consisted of 11 horizontal and 11 vertical line scans with a 5mm
136 scan length and 0.5mm interval and 6 horizontal and 6 vertical line scans with a 3mm scan
137 length and 0.5mm interval, all centered at the fovea, with a total acquisition time of 0.78
138 seconds.

139 **Data analyses**

140 - **Segmental analysis with reference to color-coded normative data**

141 The RNFL was considered abnormally thin for an individual if its value was less than the 5th
142 percentile of the age- and optic disc size-adjusted normal values and thick if it was more than
143 the 95th percentile. Abnormal thinning or thickness in at least 2 of the 4 segments within a
144 quadrant, if reproducible, was considered significant for that quadrant.

145 - **Quantitative analysis for individual quadrants**

146 Additionally, we measured the thickness of the RNFL ± 2 SD quantitatively in each of four
147 quadrants and compared these values with normative data provided to us by the company that
148 was not corrected for age and optic disc size and which was retrieved from 268 eyes of 134
149 normative control subjects (mean age of 44.1 ± 15.5 years).

150 **Statistical analysis**

151 Differences in the mean of peripapillary RNFL thickness in our study population and that
152 from the normative data were analyzed by the two-tailed Student *t*-test. A probability value of

153 less than 0.05 was considered statistically significant. Since most of participants had a
154 symmetrically equivalent RNFL thickness between eyes, the mean of RNFL thickness of
155 each patient whose scans were included for both eyes was calculated as a single number, so
156 that an analysis was performed in a by-person basis. Differences were studied for the
157 thickness in overall circumference, hemispheres (superior and inferior), and quadrants
158 (superior, nasal, inferior and temporal). The association between the presence of RNFL
159 thinning (by segmental analysis) and age was also analyzed using Fisher's Exact test in the
160 by-eye analysis.

161 **Results**

162 Twenty four patients with the diagnosis of juvenile XLRs were included in our study. We
163 included 43 eyes; 23 right eyes (53.5%) and 20 left eyes (46.5%). In 5 patients (20.8%), only
164 one eye was included due to the presence of a traumatic cataract, rotatory nystagmus, old
165 retinal detachment, or poor patient fixation which made the acquisition of a reliable RNFL
166 scan difficult.

167 The average age of the 24 patients in the study was 28.8 years \pm 14.7 years with a range from
168 10–54 years. There were 22 Caucasian (91.7%), and 2 Hispanic (8.3%) patients enrolled in
169 the study. In 14 patients (58.3%), the abnormal disease causing gene was previously
170 identified (Table 1).

171 The average best-corrected visual acuity in the right eyes was 0.50 logMAR units with a SD
172 of 0.24 (range, 0.10-1.00), equivalent to 20/25 - 20/200. The average best-corrected visual
173 acuity in the left eyes was 0.48 logMAR units with a SD of 0.24 (range, 0.04-1.00),
174 equivalent to 20/22 – 20/200.

175 The range of IOP for all patients was from 8 to 17 mmHg in the right eyes (mean, 13.0
176 mmHg, and SD of 2.4), while the range of IOP in left eyes was from 10 to 17 mmHg (mean
177 12.8 mmHg, and SD of 2.2). None of the patients had a glaucomatous appearance to the optic
178 disc. Three patients (14.3%) had mild temporal disc pallor clinically in both eyes. Two out of
179 the three patients showed thinning in the RNFL thickness in the temporal quadrants, while
180 the other patient showed thinning of the RNFL in the superior, nasal and inferior quadrants
181 with normal RNFL thickness in the temporal quadrant.

182 Among our 24 patients with XLRS, 15 patients (62.5%) showed a thinning of the RNFL in
183 one or more quadrants in at least one eye and 9 patients (37.5%) in both eyes. Thinning of the
184 RNFL in 1 quadrant was seen in 12 eyes (27.9%) of 10 patients (41.7%), and thinning in 2 or
185 more quadrants was seen in 12 eyes (27.9%) of 8 patients (33.3%).

186 Of note, the presence of RNFL thinning was present in 7 (87.5%) of 8 patients who were
187 older than 35 years of age. All of the seven patients had thinning of RNFL in at least one
188 quadrant in all studied eyes (5 patients whose both eyes were included, and 2 patients where
189 only one eye was studied). For those who were younger than 35 years old, thinning of RNFL
190 in at least one quadrant was observed in 9 (56.3%) of 16 patients. In those 9 patients, 7
191 patients were studied bilaterally, and 4 of the 7 patients showed thinning in only one eye.
192 There was a statistically significant difference for the presence of RNFL thinning in at least
193 one quadrant in the older (≥ 35 years old) compared to the younger age group (< 35 years
194 old) ($p = 0.0028$). The significant difference was still demonstrated at the cut-off age of 30
195 years old ($p = 0.0477$).

196 Regarding the distribution for abnormal thinning of the RNFL among the 4 quadrants,
197 thinning in the inferior quadrant was most commonly seen in 18 eyes (41.9%) of 12 patients

198 (50%), followed by the temporal quadrant in 12 eyes (27.9%) of 8 patients (33.3%), nasal
199 quadrant in 5 eyes (11.6%) of 4 patients (16.7%), and the superior quadrant in 5 eyes (11.6%)
200 of 4 patients (16.7%) (Figs 1-2).

201 We also found that the overall average RNFL thickness at a diameter of 3.45mm in our study
202 population to be 100.95 μm with a SD ± 16.02 , compared to normative data, where the
203 average RNFL thickness was 106.72 μm with a SD ± 11.34 . The patients with retinoschisis
204 had a statistically significant difference of mean RNFL thickness compared to the normative
205 data ($p = 0.034$).

206 By assessing the RNFL thickness quantitatively in each quadrant, compared to the values of
207 the mean RNFL thickness $\pm 2\text{SD}$ provided by the manufacturer, using the criteria of
208 calculating the average RNFL thickness $\pm 2\text{SD}$ for each quadrant, we found that 14 eyes
209 (32.6%) had statistically significant thinning of the RNFL in the inferior quadrant, while only
210 1 eye (2.3%) was found to have a thicker than normal RNFL in the inferior quadrant. We
211 additionally found that 5 eyes (11.6%) had thinning of the RNFL in the temporal quadrant
212 while 4 eyes (9.3%) were found to have a thicker than normal RNFL in the temporal
213 quadrant. We were unable to find any RNFL thickness defects in either the superior or nasal
214 quadrants by this quantitative method of analysis not accounting for age or optic disc size.

215 Further, we calculated the average RNFL thickness on all patients from all quadrants and
216 compared these values to the normative values provided by the manufacturer uncorrected for
217 age or optic disc size. As shown in Table 2, statistically significant differences in mean
218 RNFL thickness were seen only in the inferior and temporal quadrants. There were no
219 statistically significant differences in mean RNFL thickness in any quadrants, when
220 comparing between the right and left eyes (p values ranged between 0.516-0.998)

221 The overall average for the RNFL thickness in the superior hemisphere was $105.69 \mu\text{m}$ ($\text{SD} \pm$
222 15.82), while in the control group the average thickness was $106.59 \mu\text{m}$ ($\text{SD} \pm 12.68$). In the
223 inferior hemisphere the overall average was $95.43 \mu\text{m}$ ($\text{SD} \pm 17.48$), while the control group
224 was $106.84 \mu\text{m}$ ($\text{SD} \pm 11.53$). There was no statistically significant difference shown in the
225 superior hemisphere ($p = 0.7586$), but a statistical difference was demonstrated in the inferior
226 hemisphere ($p < 0.0001$).

227 All patients included in the study were also examined by FD-OCT for the presence of cystic
228 changes within the macula using the MM5 and Radial Lines examination protocols. Macular
229 cysts were observed in 29 eyes (67.4%) from 18 patients (75.0%).

230 **Discussion**

231 In our cohort of 24 patients with XLRs, 15 patients (62.5%) showed a thinning of the RNFL
232 in one or more quadrants in at least one eye by criteria referenced to color-coded normative
233 data for segments within each quadrant. Abnormal thinning was more commonly found in the
234 inferior and temporal quadrants. The nasal and the superior quadrants were equally affected
235 and both showed thinning in fewer eyes than were seen in the inferior and temporal
236 quadrants. A direct quantitative comparison between quadrants using data computed directly
237 for each quadrant also confirmed a significant reduction of mean RNFL thickness in the
238 inferior and temporal quadrants in our patients compared to normative data.

239 The segmental analysis for determining quadrant defects was based on normative data
240 corrected for age and disc size provided by the manufacturer. Due to a proprietary limitation,
241 the normal values from specific age groups were unavailable for our directly computed
242 quantitative analysis of each quadrant. The normative data used herein were retrieved from
243 visually normal subjects at a wide range of age. Therefore, the mean age of our study subjects

244 was lower than that of the normative data. However, this limitation would not likely have
245 affected our conclusions since we would more likely have anticipated a thicker RNFL in the
246 younger patients had their RNFL not been affected by their disease.²² It is possible that we
247 may have found even greater statistically significant results in our analysis if we could have
248 used data from age-similar controls in this portion of our directly computed quadrant
249 analysis.

250 The finding of changes in the RNFL of our XLRS patients might have been anticipated in
251 reference to a report by Yanoff et al.,¹⁰ which stated that the primary pathology in XLRS was
252 located in the inner retinal layers. Other previous studies based on histopathologic analysis
253 suggested that the likely primary lesion in XLRS occurs initially in the innermost portion of
254 Müller cells or at the border of the RNFL.¹⁰⁻¹²

255 Also, our finding of RNFL thinning is in agreement with previous studies by Manschot and
256 Condon et al.,¹¹⁻¹² which described optic nerve atrophy in XLRS patients. Using a time-
257 domain scanning procedure of the macula, Apushkin et al.,¹⁷ did not observe any thinning of
258 the papillo-macular bundle RNFL thickness on OCT imaging in patients with juvenile XLRS
259 and no clinical findings of optic disc pallor.

260 One of the current study's potential limitations was that the drawing of the margins of the
261 optic discs was done manually for all patients; hence, the size of the optic disc might have
262 been subjectively influenced by the operator. Further, another parameter which might have
263 influenced the RNFL thickness measured by OCT was the axial length of the eye,¹⁹⁻²¹ since
264 we did not correct for this factor in the directly computed quadrant quantitative analysis
265 portion of our study when using values for various quadrants compared to the manufacturer's
266 provided normative data that also did not correct for axial length. However, we only included

267 patients with a lower degree of refractive error in whom a normal or close to normal axial
268 length might be assumed.

269 Our study showed that older XLRS patients were more likely to show RNFL thinning which
270 suggests that the younger patients might have a higher potential to benefit from treatment.
271 This has potential significance for future treatment trials in patients with XLRS where patient
272 selection might be influenced by the degree of thinning in their RNFL. However, this
273 hypothesis needs to be confirmed in future treatment trials. Nonetheless, use of high-speed,
274 high-resolution tools such as FD-OCT may be useful to measure RNFL thickness during
275 patient selection in future therapeutic trials for patients with XLRS.

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340 **Titles and legends to figures**

341 Figure 1: Abnormal thinning in 3 of 4 segments in the temporal quadrant of the right eye in a
342 patient with XLRS. A single segment is abnormal in the inferior quadrant.

343 Figure 2: Thinning of the superior, inferior, and temporal quadrants of the RNFL in the right
344 eye of a patient with XLRS. All 4 segments in the temporal quadrant are thin while 2 of 4 in
345 the superior and inferior quadrants are thin.

346