The electrophysiological features of X-linked juvenile retinoschisis in a young male: a case report

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Abstract

This case report describes the detailed electrophysiological features and the corresponding relationship with the structural changes in a case of X-linked juvenile retinoschisis (XLRS). A 25-year-old male presented with a history of several years of decreased visual acuity in both eyes. The best corrected visual acuity was 20/200 in oculus dexter (OD) and 20/80 in oculus sinister. Retinoschisis was found in the macula by optical coherence tomography, which was more severe in OD. Electroretinogram revealed a similar electronegative waveform in both eyes. Visual evoked potential detected a reduced amplitude and delayed phase in P100-wave, which was worse in OD. The patient was diagnosed as XLRS and advised to undergo continuous medical observation. He was followed up for the next year, with no significant change in retinal function and structure being observed. These current findings suggest that electrophysiology permits the detailed analysis of the clinical picture of XLRS and helps to gain a deeper understanding of the pathogenesis.

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Introduction

X-linked juvenile retinoschisis (XLRS) is a hereditary retinal dystrophy first described in 1898 by Haas.[1] Due to the X-linked recessive inheritance, females are rarely affected.[1] XLRS is recognized as one of the most common macular degenerative diseases in young males, with a worldwide prevalence that is estimated to range from 1 in 5000 to 1 in 30 000.[2,3] XLRS can lead to progressive visual loss due to the foveal involvement.[4] The retinoschisin 1 (_RS1_) gene on chromosome Xp22 is responsible for coding for the retinoschisin protein, which is implicated in cellular adhesion and cell–cell interactions.[5] Mutations in the _RS1_ gene have been identified as the underlying cause for XLRS.[5]

The diagnosis of XLRS is often clinically obtained based on the hallmark of an intra-retinal cystoid macular space and foveal schisis. Approximately half of affected patients are also affected by peripheral retinoschisis.[6] Usually, prophylactic treatment for XLRS is not warranted.[7] Surgical interventions are necessary in the case of vitreous haemorrhage, retinal detachment or other serious conditions.[8,9] An electronegative waveform in a full-field electroretinogram (ERG; i.e. a reduction of the b-wave amplitude disproportionately to that of the a-wave) is commonly thought to be the electrophysiological signature of XLRS.[1,10] In addition to the macula cystic and peripheral schisis, splitting at the level of the nerve fibre layer (NFL) also occurs.[11] The function of the visual pathway may thus be interfered with. However, the detailed electrophysiology in XLRS, especially the visual pathway, and the corresponding relationship with the structural changes, have not been fully elucidated.

This current case report describes the visual function and the corresponding relationship with structural features in a patient with XLRS. The findings of this current case suggest that the electrophysiological analysis of XLRS may permit a deeper understanding of the pathogenesis and the structural features.

Case report

In August 2018, a 25-year-old male patient presented to the Department of Ophthalmology, The 900th Hospital of PLA, Fuzhou, Fujian Province, China complaining of many years of decreased visual acuity in both eyes. He also complained about floaters in front of both eyes. He had poor vision and had tripped over repeatedly since he was a child. He did not share any difficulties in colour vision or during night-time activities. He had no other known medical conditions. However, he did not know the exact diagnosis at that stage. His family history was negative for ocular diseases. The best corrected visual acuities were +2.50/−1.75 × 117 (20/200) oculus dexter (OD) and +2.00/−0.25 × 4 (20/80) oculus sinister (OS). Intraocular pressure values were normal in both eyes (15 mmHg OD and 13 mmHg OS; normal range, 10–21 mmHg). The anterior segment was unremarkable in both eyes, with a clear cornea, lens and anterior chamber. Pupils were equal in size, being reactive to light. No relative afferent pupillary defect was found. The Amsler chart revealed the metamorphopsia in both eyes, which was more severe in OD.

On dilated fundus examination, a round-shape darkness around the macula was presented in both eyes, with no light reflection from the fovea (Figure 1). The optic nerve head was normal. No signs of trauma, such as retinal haemorrhage, in the posterior segment were found. No neovascularization or other abnormalities were presented in the peripheral retina or elsewhere. The optical coherence tomography (OCT) scanning revealed intraretinal cystoid spaces and retinoschisis in and around the macula of both
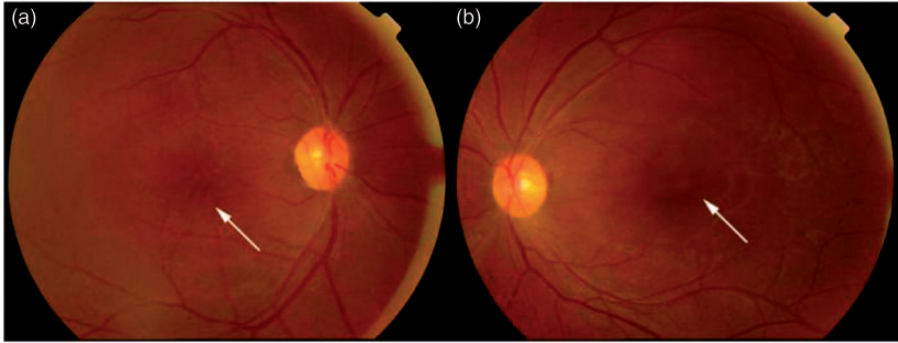
Figure 1. Dilated fundus examination of both eyes of a 25-year-old male patient that presented with many years of decreased visual acuity in both eyes: (a) the right eye; (b) the left eye. Macular oedema-like change (white arrow) was present in both eyes. The colour version of this figure is available at: http://imr.sagepub. com.

eyes, which was more severe in OD (Figure 2). No retinoschisis was found in the peripheral retina on OCT. The intraretinal separation presented mostly insides the inner nuclear layer (INL), with some in the outer nuclear layer (ONL) and the NFL. The thickness of ONL under the area of the INL separation was reduced. Alterations of the external limiting membrane, ellipsoid zone, and interdigitation zone were presented in both eyes, while no epiretinal membrane or posterior vitreous detachment was found.

The full-field ERG performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standard revealed an obvious decrease in the b-wave amplitude in dark-adapted 3.0 and 10.0 responses (Figure 3). [12] The b-wave amplitude in the dark-adapted 0.01 and light-adapted responses was also reduced to some extent. The a-wave amplitude was almost unchanged in all ERG responses compared with that of the b-wave, comprising the so-called electronegative ERG. The b/a ratio in the dark-adapted 10.0 response was 0.641 in OD and 0.611 in OS, which were beyond the normal range of 1.50–2.60. In addition, the oscillatory potentials response was markedly accentuated with no discernible waveforms. There were no significant differences for all the parameters of ERG between OD and OS. The pattern visual evoked potential (PVEP) test was also recorded according to the ISCEV standard (Figure 4). Delay of the peak time of P100-wave in the 1 degree (1°) and 0.25° responses was found in both eyes. Both amplitudes of P100-wave were reduced, with the amplitude of OD significantly lower than that of OS.

The patient was diagnosed with XLRS on the basis of the typical phenotype of the retinoschisis under OCT and the electronegative ERG. Genetic analysis of the mutation sites in the *RS1* gene is extremely useful for the diagnosis of XLRS because they are the underlying cause of XLRS.[13] However, it was not performed for this current case due to his restricted financial ability. He was advised to undergo medical observations and to return to the clinic if his vision worsened suddenly or more floaters were noted. No special medication was prescribed. The patient was followed up for the next year and there was no change in visual acuity or the extent of retinoschisis. No significant change of the retinal function and structure was observed. Ongoing medical observations were advised.
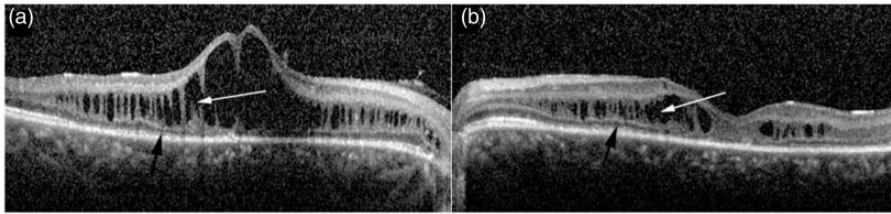
Figure 2. Optical coherence tomography (OCT) scanning of both eyes of a 25-year-old male patient that presented with many years of decreased visual acuity in both eyes: (a) the right eye; (b) the left eye. OCT showed macular schisis and extramacular intraretinal separation (white arrow), which was more obvious in the right eye. Alterations of the external limiting membrane, ellipsoid zone and interdigitation zone (black arrow) were also found in both eyes.
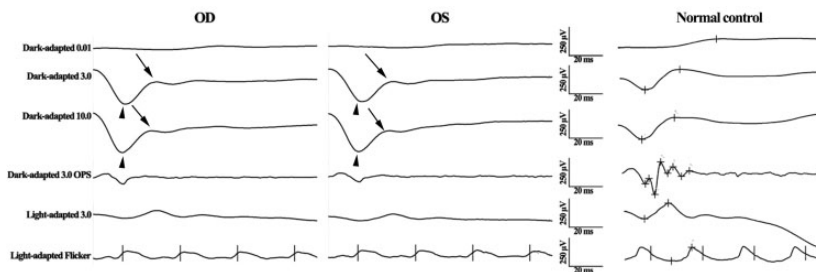

Figure 3. Full-field electroretinogram of both eyes of a 25-year-old male patient that presented with many years of decreased visual acuity in both eyes: (A) the right eye; (B) the left eye. Absence of the scotopic b-wave (black arrow) and a nearly normal a-wave (black arrowhead) were presented. The parameters were comparable for both eyes. The vertical scale measures the amplitude; the horizontal line measures the peak time. Six responses of electroretinogram according to the International Society for Clinical Electrophysiology of Vision standard: dark-adapted 0.01, dark-adapted 3.0, dark-adapted 10.0, dark-adapted 3.0 oscillatory potentials (OPS), light-adapted 3.0 and light-adapted 3.0 flicker. OD, oculus dextrus; OS, oculus sinister.

The Ethics Committee of the 900th Hospital of PLA approved the publication of this case report (no. 202108070018). Written informed consent was obtained from the patient and his family for his anonymized data to be published in this article. The reporting of this study conforms to CARE guidelines.[14]

Discussion

Intraretinal cysts at the fovea, the so called retinoschsis, are the pathophysiological morphology of XLRS, which is sometimes accompanied by peripheral retinal schisis.[15] Macular schisis is sometimes difficult to distinguish under ordinary fundus examination from macular oedema caused by other ocular diseases, such as central serous choriodoretinopathy, diabetic macular oedema or pseudophakic cystoid macular oedema.[16] With the advent of OCT, the characterization of *in-vivo* retinal structure has greatly aided in the diagnosis of XLRS.[4] The OCT results for the current case clearly revealed macular schisis in
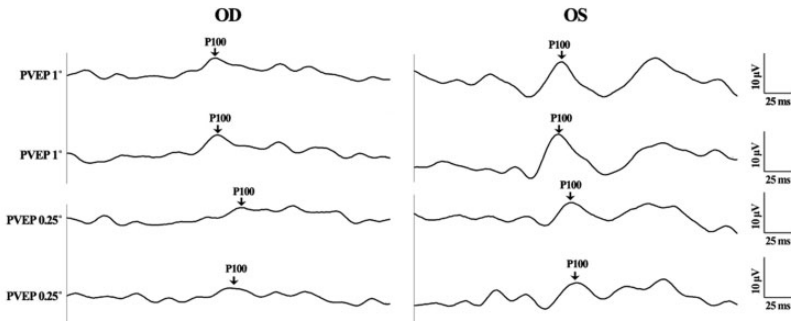
Figure 4. Pattern visual evoked potential (PVEP) test of both eyes of a 25-year-old male patient that presented with many years of decreased visual acuity in both eyes. A reduced amplitude and a delayed phase of P100-wave was found, which was worse in the oculus dextrus (OD). Arrow: the position of P100. The vertical scale measures the amplitude; the horizontal line measures the peak time. PVEP 1°, 0.25°: the spatial frequency of pattern used in the PVEP examination. OS, oculus sinister.

both eyes. In addition, macular schisis and intraretinal separation were observed to be worse in OD. OCT could also help to recognize the involvement and the damage of the retinal layer. The results from a series of cases revealed the wide schisis cavity under the macular area, intrafoveal and perifoveal retina, and a cleavage plane in both the nerve fibre and outer retinal layers.[17] These OCT features help to predict the surgical outcome and explain the recovery of vision in XLRS cases.[18]

In addition to OCT, ERG has been of considerable value in the diagnosis of XLRS for several decades.[19] A reduction in the b-wave amplitude elicited by a bright flash of light in the dark-adapted retina (i.e. the so-called electronegative ERG) is commonly considered to be characteristic of XLRS.[1,10] Photoreceptors and bipolar cells are primarily affected in XLRS, which might be attributed to the structural defect and the synaptic changes between the photoreceptors and bipolar cells caused by the mutated *RS1* gene.[1,20] The significant decreased b-wave amplitude presented in dark-adapted 3.0 and 10.0 ERG of this current case was in accordance with the electronegative ERG of XLRS.

The b-wave reduction of ERG in XLRS has also been explained by biochemical synaptic changes that are independent of the morphological changes.[21] It is reported that most XLRS patients exhibit the 'negative' ERG while they do not exhibit extensive extramacular splitting.[4] The current ERG results support the above phenomenon, as the retinal schisis was just confined to the posterior of the retina. Furthermore, the current study found that the b-wave still existed in light-adapted ERGs with a reduced amplitude. Meanwhile, a significantly reduced b-wave in dark-adapted 3.0 and 10.0 ERGs was found. This indicates that the scotopic ERG is more affected than the photopic ERG in XLRS. A previous report argued that no specific impairment of cone-photoreceptor function in XLRS existed as the authors found that the cone sensitivity remained the same in XLRS.[22] The almost unchanged a-wave in the current case suggests that photoreceptors might not be significantly affected, which is in agreement with the previous report.[22]

Even though being a key diagnostic parameter for XLRS, the eletronegative ERG is present in about half of all patients.[23] Dysfunction of the inner retina in congenital stationary night blindness and

acquired conditions like central retinal artery occlusion could also present with an electronegative ERG.[24] Extra caution is advised when analysing the ERG data in the diagnosis and evaluation of interventions in patients with XLRS.[25]

In greater detail, intraretinal cysts were found in the NFL from the OCT scanning of both eyes of the current case. Anatomical splitting through the NFL and thinning of the NFL were previously reported in XLRS.[26] It is likely that the function of the visual transduction may also be interfered with in XLRS. The reduced amplitude and delayed phase of P100-wave in PVEP from this current patient confirmed this hypothesis. The ERG parameters in the current case were quite comparable in both eyes, although the extent of the macular schisis was not. This phenomena might be a bit different from that of a previous study, which suggested that the characteristics of one eye mirrored the structural and functional findings in the fellow eye.[20] The more severe changes to the PVEP parameters in OD in the current case were somewhat in accordance with the worse visual acuity and the morphological changes observed on OCT. PVEP was also performed in another case of XLRS, while the detailed features were not described.[27] The interpretation of the abnormal PVEP in this current case was more comprehensive and indicates that PVEP might help in the evaluation of the functional progress of XLRS, in addition to ERG.

In conclusion, this current report describes a case of XLRS with a detailed description of their retinal function as demonstrated by ERG and PVEP in addition to the retinal morphological changes. The accurate diagnosis of XLRS is required before treatments can be prescribed. The availability of electrophysiological analysis of XLRS could help to gain a deeper understanding of its clinical picture and underlying pathogenesis.

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