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SHORT COMMUNICATION

Identification of XLRS1 gene mutation (608C>T) in a Portuguese family with juvenile retinoschisis

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PURPOSE. To characterize electroretinogram (ERG) and molecular genetic findings in a family with XLRS1 mutation. The authors present two cases of a Portuguese family with juvenile retinoschisis with a mutation in exon 6.

METHODS. Two brothers and their parents, grandmother, and uncle underwent a full ophthalmic examination. The two brothers with ophthalmic disease were evaluated with color fundus photography, fluorescein angiography, optical coherence tomography (OCT), molecular genetic study (Group VI of Retinoschisis Consortium), pattern visual evoked potential (PVEP), and full field ERG.

RESULTS. Both patients presented funduscopic manifestations of vitreoretinal degeneration. They presented peripheral schisis and retinal detachment. However, foveal schisis had never been observed at funduscopy. A negative ERG was recorded in both. Six months after that, the younger brother showed a typical foveal schisis at fundus examination. A retinoschisis gene (XLRS1) mutation with transition of cytosine by thymine at position 608 (608C>T) had been identified in both.

CONCLUSIONS. Negative ERG is the most secure clinical marker to establish the diagnosis of juvenile retinoschisis. XLRS1 gene 608C>T mutation was described for the first time in a Portuguese family. (Eur J Ophthalmol 2005; 15: 638-40)

KEY WORDS. Hereditary vitreoretinal disease, Negative ERG, Retinoschisis Consortium (exon 6 mutations), X-linked juvenile retinoschisis, XLRS1 gene mutation

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INTRODUCTION

Juvenile retinoschisis is an X-linked disease caused by a mutation in retinoschisis gene (XLRS1) and it affects male patiens (1, 2). There is a cleavage at the level of retinal fiber nerve layer, due to Müller cells defects (2, 3). Recent studies showed photoreceptors and bipolar cells were primarily affected (4). We report two male brothers with atypical phenotype and without family history of this disease.

METHODS

Two brothers and their parents, grandmother, and uncle underwent a full ophthalmic examination. The two brothers the only ones with ophthalmic disease were evaluated with color fundus photography, fluorescein angiography, optical coherence tomography (OCT), molecular genetic study (Group VI of Retinoschisis Consortium), pattern visual evoked potential (PVEP), and full field electroretinogram (International Society for Clinical Electrophysiology of Vision (ISCEV) standard).

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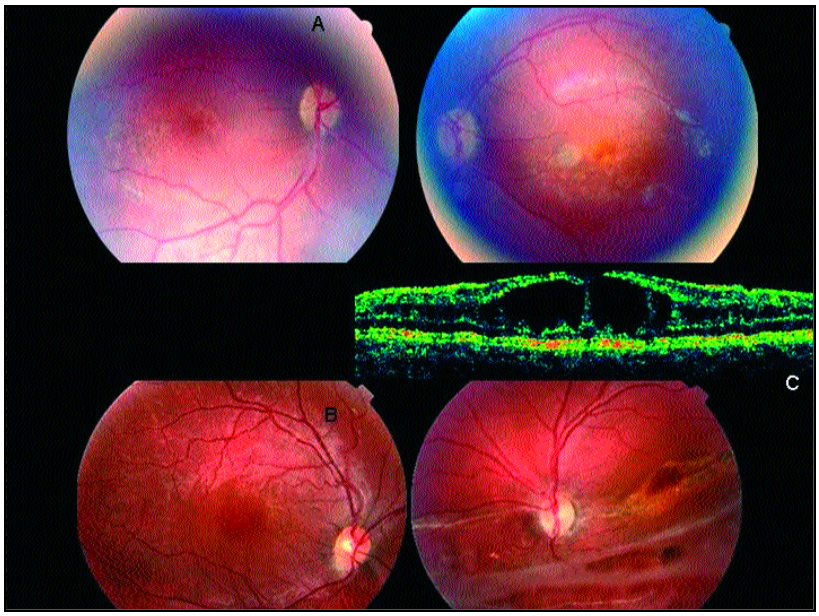

Fig. 1 - (A) Case 1 color fundus photography: bilateral vitreous densifications, several pigmentary macular changes, and "hammed-copper" peripheral retina, without macular schisis. **(B)** Case 2 color fundus photography: right typical foveal schisis, left vitreous densifications and pigmentary macular changes. **(C)** Case 2 foveal schisis (optical coherence tomography image): separation between neurosensorial retina, with an internal "detached" layer and an external moderate reflectivity layer beneath retinal pigment epithelium and columnar tissue between two layers.

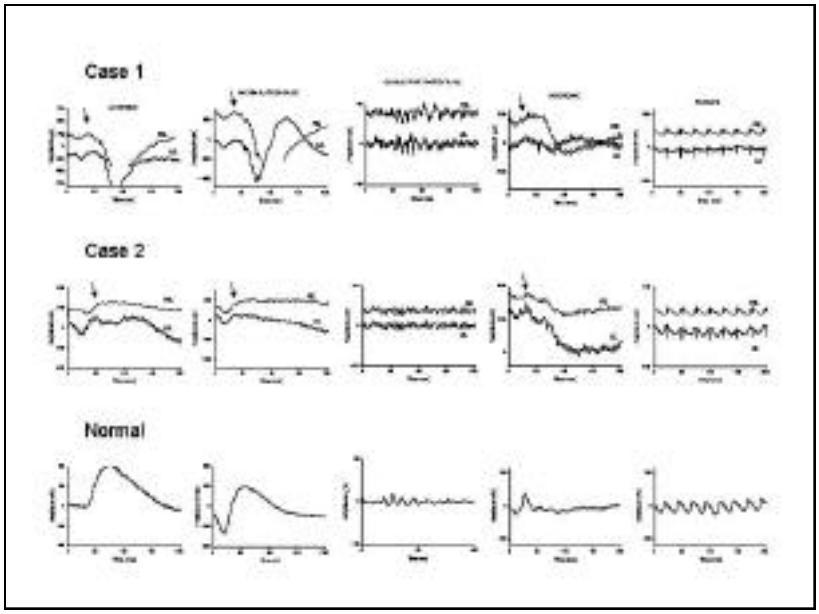

Fig. 2 - Case 1 and Case 2 negative electroretinogram: normal a wave and b wave markedly reduced (arrow). Normal electroretinogram to compare.

RESULTS

The parents of these boys and two family members of their mother (grandmother and uncle) had normal results on ophthalmic examination.

Case 1

A boy presented to the emergency room at 8 years of age because of decreased visual acuity (VA) after blunt trauma. He presented left eye (LE) esotropia, nystagmus, and right eye (RE) retinal detachment. A RE scleral buckle was implanted. After loss of follow-up for 5 years, his best-corrected VA was 20/70 (RE) and 20/100 (LE), he showed RE inferotemporal retinoschisis, both eyes (OU) had vitreous densifications, and several pigmentary macular changes and "hammed-copper" peripheral retina were noted, without macular schisis (Fig. 1A). Some weeks later, he presented with a new RE retinal detachment treated by pars plana vitrectomy and silicone oil tamponade. Electroretinogram (ERG) showed negative pattern (Fig. 2). On ERG basis, we made diagnosis of X-linked juvenile retinoschisis.

Case 2

A male patient, brother of the propositus, came to clinics at 3 years of age with OU macular and peripheral pigmentary changes and RE peripheral retinoschisis.

After 5 years loss of follow-up, he showed nystagmus, LE esotropia, and peripheral retinoschisis. ERG revealed no negative pattern. Some weeks later, he came to the emergency room with LE retinal detachment and vitreous hemorrhage LE scleral buckle was implanted. One year after surgery, he presented best-corrected VA 20/50 (RE) and 20/80 (LE) and negative ERG (Fig. 2). Six months later, we observed a typical foveal schisis (Fig. 1B) confirmed by OCT (Fig. 1C). An exon 6 mutation with transition of cytosine by thymine at position 608 (608C>T) of XRLS1 gene was identified in both patients, using methodology described by Dr. Trump et al (5).

DISCUSSION

Macular changes are present in almost all patients. While younger patients show typical foveal schisis, older ones present atrophic changes (5-7). Foveal schisis is always difficult to see. However, it can be clarified, in vivo, by OCT.

Pathophysiologically, retinoschisis originates by the separation within neurosensorial retina, with an internal "detached" layer and an external layer beneath retinal pigment epithelium and columnar tissue between these two layers (8). Case 1 never showed foveal schisis and Case 2 revealed it after electrophysiologic diagnosis (Fig. 1). Atypical clinical presentation of juvenile retinoschisis makes ERG essential to diagnosis (3, 6). ERG findings suggested a primary defect at Müller cells level because b wave is generated by bipolar cell's depolarization and Müller cell (4, 7). Scotopic ERG is more affected than photopic: typically, a wave has normal amplitude and b wave is markedly reduced (negative ERG). XLRS1 gene locates at short arm of X-chromosome (Xp22.2). Its mutations lead to structural defect of photoreceptors and bipolar cells. This gene expresses only in retina as a 224 aminoacids surface protein (retinoschisin) which keeps adhesion between retina cells. Our patients have an exon 6 mutation with transition of cytosine by thymine at position 608 of DNA. This exchanges proline by leucine at codon 203 of retinoschisin. This 608C>T mutation was described for the first time in a Portuguese family (5). Juvenile retinoschisis fundus has a broad spectrum. It is important to add general ophthalmic examination with ERG, OCT, and molecular genetics for earlier diagnosis and prognosis.

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