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EXPANDING THE PHENOTYPIC SPECTRUM OF CONGENITAL X-LINKED RETINOSQUISIS

Nathália Nishiyama Tondelli, Beatriz Mello Mencaroni , Carolina Maria Barbosa Lemos, Gabriel Castilho Sandoval Barbosa, Jefferson Rocha de Sousa, André Marcelo Vieira Gomes, Mariana Matioli da Palma.

Instituto Suel Abujamra

PURPOSE

Describe the atypical association of retinal exudation in a clinical and molecular diagnosis of XLRS to broaden the spectrum of this rare disease.

INTRODUCTION

X-linked retinoschisis (XLRS) (OMIM 312700) is a rare infantile retinal dystrophy with estimated prevalence ranging from 1:15,000 to 1:30,000 [1]. The disease occurs due to variants of the RS1 gene (OMIM 300839), which encodes a cell surface adhesion protein called retinoschisin. According to the Human Gene Mutation Database, more than 240 RS1 variants have been associated with retinoschisis (http://www.hgmd.cf.ac.uk/).

Clinical symptoms generally appear in boys in the first year of elementary school and range from mild to severe low visual acuity with central involvement.

The hallmark of congenital retinoschisis is a foveal schisis presented as a spoked wheel pattern on fundus examination. Peripheral retinoschisis can also occur and, in rare cases, extend to the fovea. Histopathologic studies reported schisis involving the retinal nerve fiber layer (NFL).

Atypical phenotypes associated with XLRS have also been reported in the literature, such as macular hole, peripheral schisis without macular schisis, vitreous veils without retinoschisis and retinal angioma. In 1998, Fong described an unusual occurrence of massive Coats-like retinal detachments in two patients with a clinical diagnosis of X-linked retinoschisis.

METHODS

This is a case report approved by the Research Ethics Committee of the Suel Abujamra Institute of an atypical phenotype of X-linked retinoschisis associated with Coats. The patient, his mother and his younger brother underwent the necessary tests. Genetic counseling was provided.

RESULTS

A 14-year-old male patient, born at term, with no complications during delivery, came to the service with a diagnosis of Coats disease in the right eye treated with peripheral retinal laser in both eyes at another outpatient clinic two years ago. His mother reported that he had difficulty seeing well since he was six years old. Infectious serologies were negative. His best corrected visual acuity was 1 foot in the right eye and 20/40 in the left eye.

Fundus examination of the right eye showed an area of exudation and retinal detachment in the posterior pole and inferiorly. (Figure 1). The left eye showed cystic changes in the fovea in a spoked wheel pattern, presence of laser scars from panretinal photocoagulation. Angiofluorosceinography showed dilated and tortuous vessels, in addition to peripheral temporal leakage in the right eye. Optical coherence tomography revealed diffuse schitic cavities in the left eye. Ocular ultrasound excluded a vascular tumor in the right eye (Figure 2).

The mother did not present anything noteworthy on the exams. Fundus examination of the 6-month-old brother revealed abnormal foveal reflex and vessels exiting the optic disc at ninety degrees and peripheral bullous retinoschisis in the right eye.

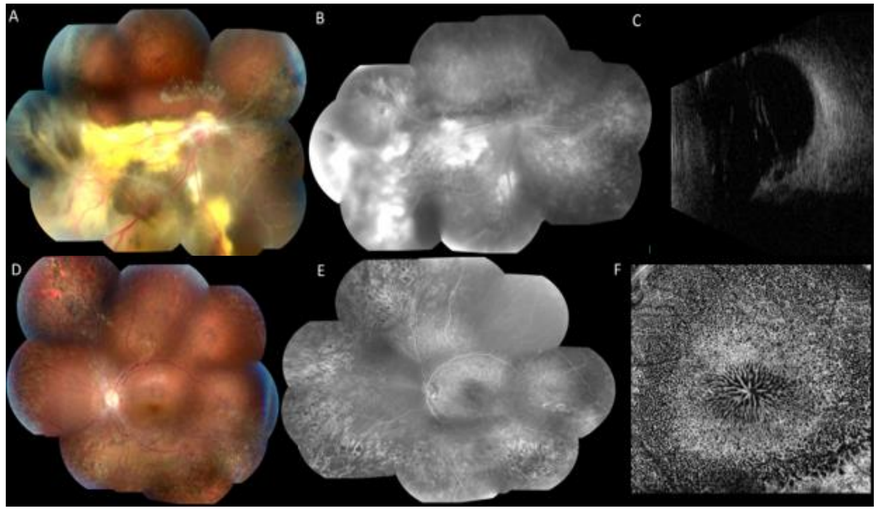

Figure 1: Multimodal imaging in a patient with hemizygous pathogenic variant in RS1 c.304C>T (p.Arg102Trp).

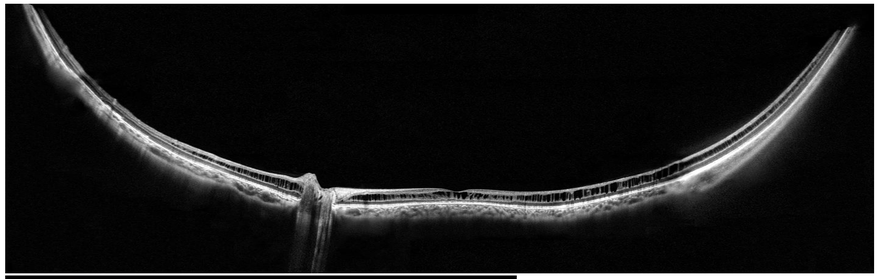

Figure 2: Optical coherence tomography montage revealed the presence of diffuse schitic cavities in the left eye.

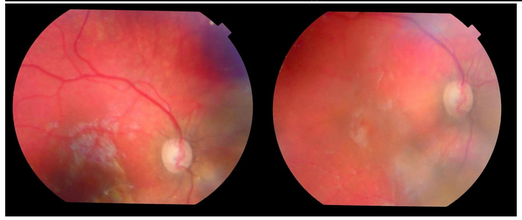

Figure 3. Fundus image of the patient's younger brother

The next generation sequencing panel found a hemizygous missense variant in RS1 c.304C>T (p.Arg102Trp) that was classified as pathogenic. This variant was found in both the patient and his younger brother.

The next-generation sequencing panel, targeting hereditary retinal diseases, included CRB1 which has previously been associated with Coats type and genes that cause familial exudative vitreoretinopathy such as NDP, FZD4, LRP5, TSPAN12 and ZNF40.

DISCUSSION

The RS1 gene consists of six exons that encode 224 amino acids. Exons 1-3 tend to have nonsense mutations, while exons 4-6 have nonsense mutations. The missense variant c.304C>T (p.Arg102Trp) found in our patient alters an evolutionarily conserved position in exon 5, resulting in loss of protein function.

XLRS is one of the most common causes of juvenile macular degeneration in the disease. Therefore, Stargardt disease, the most common hereditary macular dystrophy caused by ABCA4 variants, should be considered in the differential diagnosis.

In addition, Goldmann-Favre syndrome, Wagner disease, nonhereditary idiopathic stellate foveomacular retinoschisis, and familial exudative vitreoretinopathy should also be considered as differential diagnoses.

Unilateral sheath-like exudative vasculopathy has already been reported in patients with retinitis pigmentosa (RP) due to the CRB1, CNGB1, RPGR, and TULP1 variants that were tested in our patient.

All of these diseases must be considered, but they cannot cause the typical foveal wheel seen in the left eye due to mutations in RS1 which encodes an extracellular adhesion protein that stabilizes the overall architecture of the retina.

In 1998, Fong and colleagues first reported two patients with a clinical diagnosis of congenital retinoschisis and massive exudative detachment similar to Coats' disease. It was suggested that the exudation was due to serum leakage caused by peripheral vascular incompetence. Furthermore, in a retrospective cohort study of 340 patients with XLRS, Coats-like lesions were found in 1.2% (3). The loss of retinoschisin function that leads to foveal retinoschisis can also lead to vascular anomalies. On the other hand, peripheral vascular anomalies can lead to hypoxia that can contribute to the formation of peripheral schisis.

We describe an atypical phenotype associated with c.304C>T (p.Arg102Trp) in the RS1 gene adding new insights into this rare disease.

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