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Case report

Clinical features of a toddler with bilateral bullous retinoschisis with a novel *RS1* mutation

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ABSTRACT

Purpose: To report the clinical and genetic findings of a male toddler who presented bilateral bullous retinoschisis with a novel *RS1* mutation.

Observations: This is an observational case report of a patient referred to our hospital with esotropia. A comprehensive ophthalmic examination was performed with the boy (age, 1 year 4 months) under general anesthesia that included fundus examinations, fluorescein angiography (FA), swept-source optical coherence tomography (SS-OCT), and full-field electroretinography (FF-ERG). Genetic analysis of the coding region in the *RS1* gene was performed by Sanger sequencing for the patient and mother. There was a family history of X-linked retinoschisis (XLRS). Fundus examinations and FA showed bullous retinoschisis bilaterally in the inferior retina. The SS-OCT images showed two kinds of schisis in the inner nuclear layer (INL) and more proximally. In general, the inner plexiform layer, ganglion cell layer, and retinal nerve fiber layer are in the proximal INL; however, in this case there was hyperreflective tissue with a rough surface instead of normal retinal layers. In addition, in the schisis cavity between the hyperreflective tissue and separated retina, a number of hyperreflective fiber-like strands arose from the hyperreflective tissue and extended to the schisis cavity. During the follow-up period, the bullous retinoschisis collapsed spontaneously in the right eye. FF-ERG showed a reduced b-wave and relatively preserved a-wave in all components. Genetic analysis showed a novel *RS1* mutation (c.185_186insT, p.E62DfsX24 in exon 4) in the patient and mother.

Conclusions and importance: We report the detailed retinal structure in a genetically identified case of bullous retinoschisis. The notable finding was that the cavity of bullous retinoschisis contained a number of fiber-like strands as observed in the cavity of typical retinoschisis.

1. Introduction

X-linked retinoschisis (XLRS) is a hereditary retinal disorder with characteristic foveal and peripheral retinopathy caused by splitting of the retinal layers.[1,2] In most cases, the X-linked inheritance pattern and *retinoschisin 1* (*RS1*) gene causes XLRS.[3]

Previous studies have investigated the genotype-phenotype correlation between the severity of the XLRS phenotype and *RS1* mutations, and the studies have concluded that there is little or no relationship between them.[4,5] Even in the same family, the severities of XLRS differ.[4] Although XLRS generally is diagnosed in school-age children due to moderate visual loss,[6] several cases have been reported with severe phenotypes of bullous retinoschisis with and without vitreous hemorrhage in infants.[7–9]

In this study, we reported a male toddler who presented bilateral bullous retinoschisis with a novel *RS1* mutation. The purpose of this study was to report the retinal structure and function with bullous retinoschisis.

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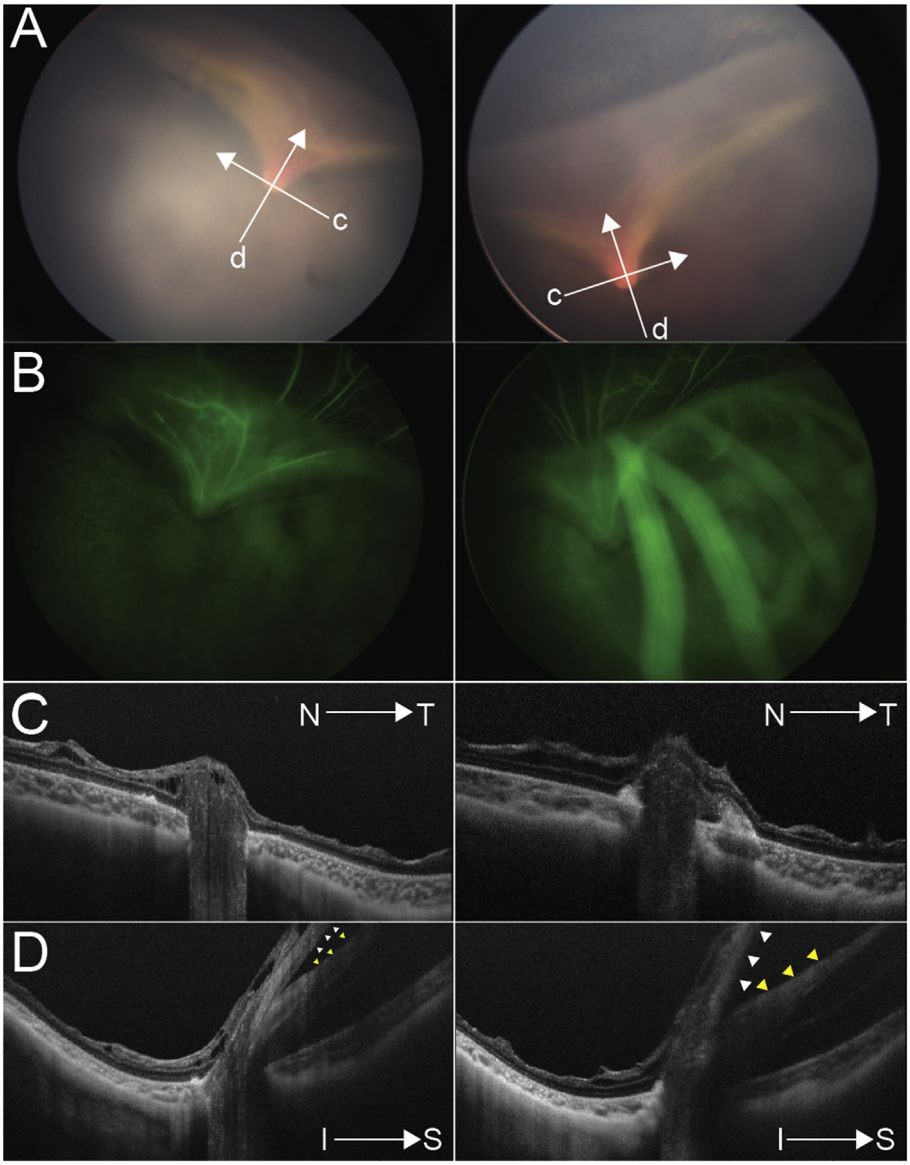

Fig. 1. Ophthalmic findings obtained from a 1 year 4 month-old boy with X-linked retinoschisis. A: Fundus photographs; B: fluorescein angiography (FA); and C and D: optical coherence tomography (OCT) images. The white arrows (c and d) correspond to the lines of the OCT scans (C and D) in each columns. The left and right columns are from the images of the right and left eyes, respectively. (A) Fundus photographs show bullous retinoschisis mainly in the inferior retina and the retina that is separated from the inferior retina covered the superior retina bilaterally and symmetrically. (B) FA show the separated retina contains the retinal vessels. (C and D) In OCT images, both naso-temporal and infero-superior sections demonstrated that retinal layers of remained inferior retina includes the retinal pigment epithelium to the inner nuclear layer with partial inner nuclear layer schisis. In addition, on those retinal layers, there remain hyper reflective tissue with rough surface. (D) White arrow heads show the separated retina from the inferior retina. Yellow arrow heads show the superior retina but the detailed retinal layers cannot be well evaluated. N = nasal, T = temporal, I = inferior, S = superior. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2. Case report

The patient was a boy at the age of 1 year and 4 months and referred to our hospital due to esotropia. He had a family history of XLRS; his male cousin was diagnosed with XLRS in Yokohama City University Medical Center and his grandfather had low vision, although ophthalmic examinations had not been performed. With the child under general anesthesia, slit-lamp examination identified thin membranous tissue with vessels behind the lens. The findings on fundus examinations showed bullous retinoschisis mainly in the inferior retina and the retina that was separated from the inferior retina covered the superior retina bilaterally and symmetrically (Fig. 1). Swept-source optical coherence tomography (SS-OCT) differentiated the retinal layers from the retinal pigment epithelium (RPE) to the inner nuclear layer (INL) with partial INL schisis at the inferior retina. In general, the inner plexiform layer (IPL), ganglion cell layer (GCL) and retinal nerve fiber layer (RNFL) are in the proximal INL; however, there was hyperreflective tissue with a rough surface on the INL layer and the hyperreflective tissue was not distinguishable into IPL, GCL, and RNFL in the current case (Fig. 1). Hence, the hyperreflective tissue and separated retina might have originated from the IPL, GCL, and RNFL. In addition, in the schisis cavity between the remaining hyperreflective tissue and separated retina, a number of hyperreflective fiber-like strands arose from the hyperreflective tissue and extended to the schisis cavity (Fig. 2, Supplemental Video).

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.ajoc.2016.12.009.

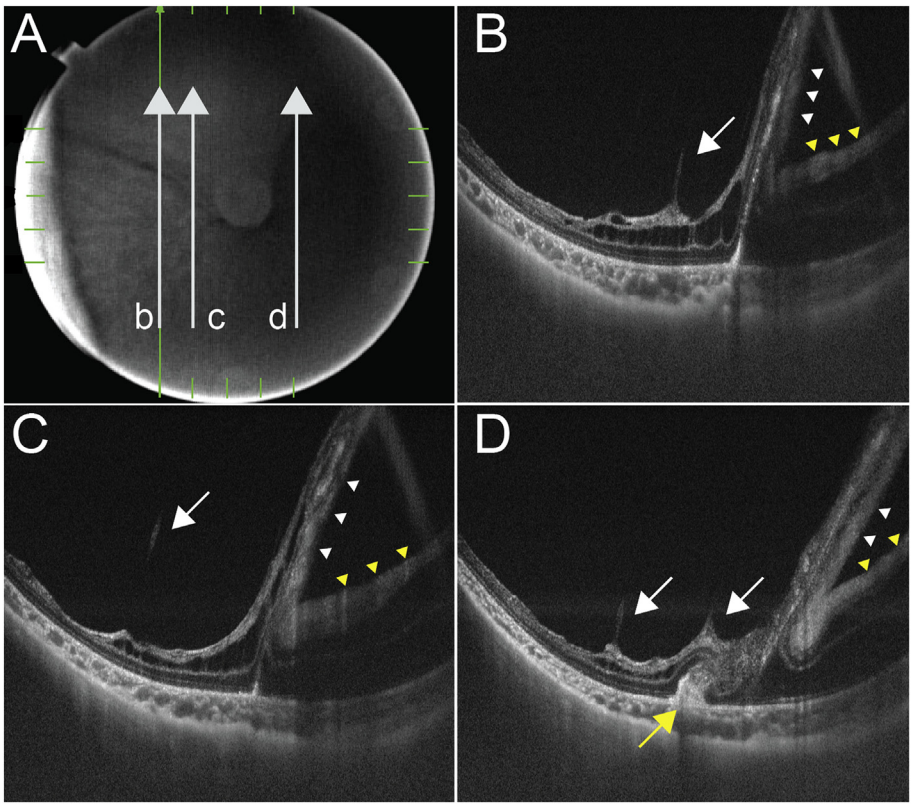

Fig. 2. Optical coherence tomography (OCT) images of the right eye obtained from a 1 year 4 month-old boy with X-linked retinoschisis. A: Infrared reflectance imaging and B, C, D: three vertical OCT scans are shown. The arrows in A (b, c, and d) correspond to the lines of the OCT scans (B, C, and D), respectively. (B, C, and D) On the remained retina from retinal pigment epithelium to the inner nuclear layer with partial inner nuclear layer schisis, there remain hyper reflective tissue with rough surface. In the schisis cavity of bullous retinoschisis, hyperreflective fiber-like strands are originated from the notch of the hyperreflective tissue (white arrows). White arrow heads show the separated retina from the inferior retina. Yellow arrow heads show the superior retina but the detailed retinal layers cannot be well evaluated. (D) The yellow arrow indicates the hump of the retinal pigment epithelium.

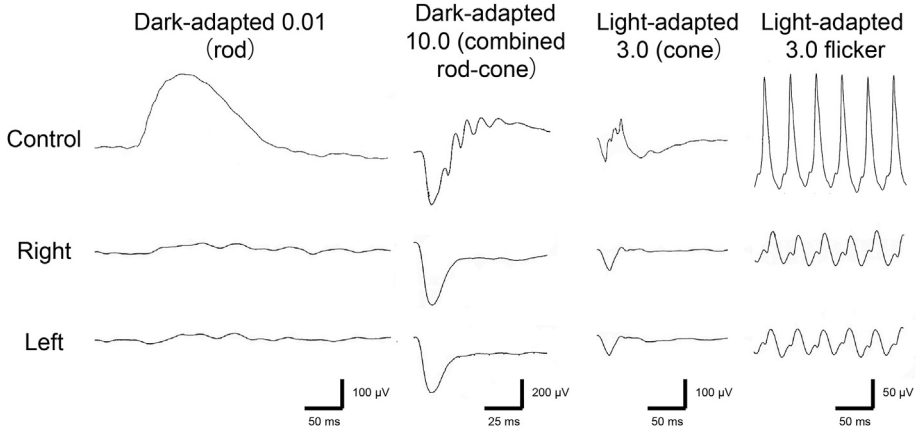

Fig. 3. Full-field electroretinography of the affected boy and control. The waves of the control are shown in the upper row. Those of the right and left eyes are shown in the middle and lower rows, respectively. The negative b-pattern is shown in the combined rod-cone response. Other clinical findings are described in the case presentation.

SS-OCT also confirmed retinoschisis in the superior retina that was covered by the separated retina from the inferior retina (Fig. 1). The hump of the RPE was partly visible at the edge of the bullous retinoschisis (Figs. 1 and 2). Full-field electroretinography (FF-ERG) showed an almost diminished b-wave in the rod response, a negative b-wave pattern with a preserved a-wave in the combined rod-cone response, a reduced b-wave and photopic negative response in the cone response, and reduced amplitudes of the 30-Hz flicker response (Fig. 3). During the follow-up period, the bullous retinoschisis collapsed spontaneously in the right eye (Fig. 4) and remained in the left eye.

Comprehensive ophthalmic examinations were performed with the child under general anesthesia including hand-held slit-lamp examination, fundus examinations, fluorescein angiography, SS-OCT (DRI OCT-1, Topcon, Tokyo, Japan), and FF-ERG. SS-OCT was performed with the patient in the supine position and with the face

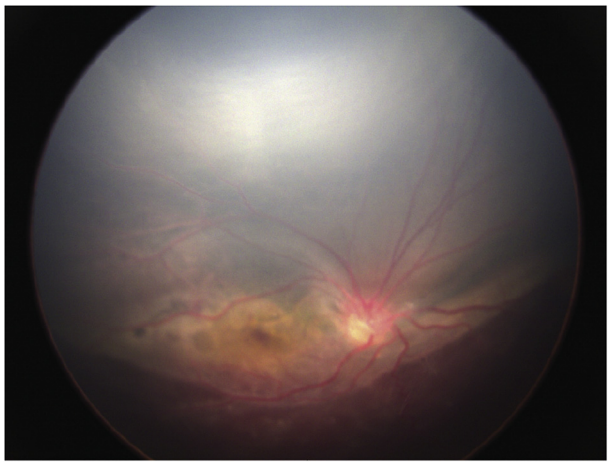

Fig. 4. A fundus photograph obtained during the follow-up period. Spontaneous improvement of the bullous retinoschisis is shown in the right eye at the age of 1 year and 7 months.

turned toward the left. The stimulus conditions of FF-ERG were set according to the guidelines of International Society of Clinical Electrophysiology of Vision.[10] The details of the procedure and conditions have been reported previously.[11]

Genetic analysis identified a novel *RS1* mutation (c.185_186insT) in exon 4, which resulted in truncated protein (p.E62DfsX24) in the patient and mother (Fig. 5). This novel *RS1* mutation was not found in the Single Nucleotide Polymorphism Database, the 1000 Genomes database, the Human Genetic Variation Browser, or Leiden Open Variation Database (version 2.0 Build 36; http://grenada.lumc.nl/LOVD2/eye/home.php?select_db=RS1). The novel *RS1* mutation (c.185_186insT) located in the acceptor cite of exon 4 (Fig. 5), in silico programs predicted that the *RS1* mutation had the potential of splicing change in Human Splicing Finder program but result in no splicing change in other two programs.

Genetic analysis of the coding region, exons 1 to 6, in the *RS1* gene was performed in the patient and mother by Sanger sequencing using the primer pairs previously reported.[12] We used accession number (NM_000330.3) of the *RS1* mRNA as the reference sequence from the National Center for Biotechnology Information. As the splice site prediction tools, we used three in silico programs; Human Splicing Finder (http://www.umd.be/HSF3/), NNSPLICE (http://www.fruitfly.org/seq_tools/splice.html), and Net Gene2 server (http://www.cbs.dtu.dk/services/NetGene2/).

3. Discussion

The splitting of the retinal layers, which can be evaluated in detail using OCT, is a characteristic finding of XLRS and has been reported in varying retinal layers from the RNFL to the outer nuclear layer.[13–15] In the current case, two types of schisis were seen in the SS-OCT images. Although one was INL schisis with a general appearance, the other was surprisingly characteristic. In the schisis cavity of bullous retinoschisis, a number of hyperreflective fiber-like strands were seen. Because there appeared to be no layers other than the retinal nerve fibers which became a number of hyperreflective fiber-like strands among the inner retinal layers, the hyperreflective fiber-like strands might be the retinal nerve fibers. In addition, FF-ERG showed preserved photoreceptor cell function but severely affected bipolar cell function with a negative b-pattern in both the rod and cone photoreceptor pathways. Although bullous retinoshisis existed bilaterally, the phenotype of the current case was in line with that of XLRS.

To date, 196 *RS1* mutations are registered in the Leiden Open Variation Database. Of those, about 40% of the mutations are considered to result in null *RS1* expression.[6] Our novel *RS1* mutation (c.185_186insT) also was predicted to result in null expression (p.E62DfsX24) or might result in null or severely damaged expression due to the splicing change, because the novel *RS1* mutation was located in the exon-intron boundary of exon 4. However, the null or severely damaged *RS1* expression could not explain the early-onset and severe phenotype in the current case because few or non-significant genotype-phenotype correlations have been reported among *RS1* mutations.[4,5] Previous studies have reported several cases with bullous retinoschisis and the identified *RS1* mutations differed.[7–9] Interestingly, these cases also showed bilateral bullous retinoschisis that resembled that of the current case. Despite different *RS1* mutations, these symmetrical and severe phenotypes between both eyes in previous and current studies were confirmed,[8,9] which suggested that additional co-factors are involved in the characteristic phenotype. There are several limitations for investigation of the cause and management, and structural analysis especially in separated and superior retina because this is a single observational case report and short follow-up period. Further study is necessary to clarify the cause and management in the cases with bullous retinoschisis.

4. Conclusions

In this study, we reported the detailed retinal structure and function in a toddler with bilateral bullous retinoschisis and a novel

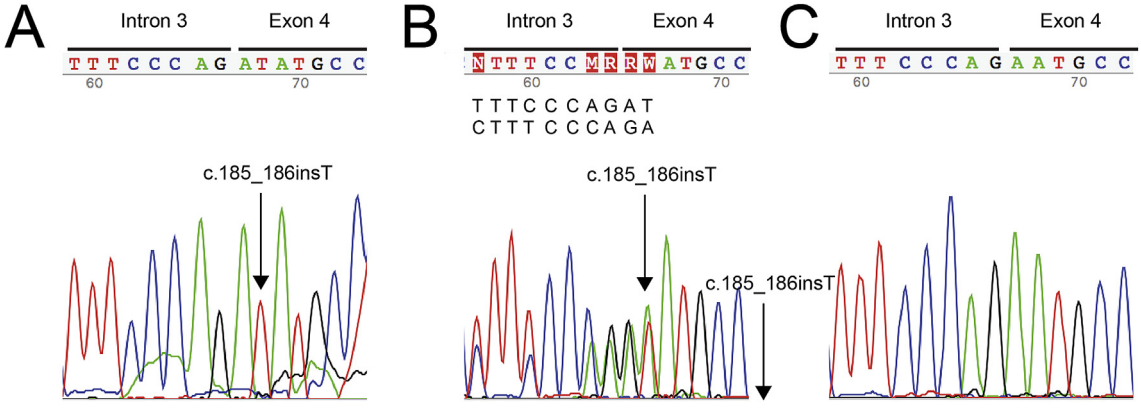

Fig. 5. The nucleotide sequence data of the identified novel *RS1* mutation. Partial reverse complementary sequences of exon 4 in A: the patient, B: his mother, and C: the control. The novel heterozygous *RS1* mutation (c.185_186insT) is identified in the patient and in his mother.

RS1 mutation (c.185_186insT, p.E62DfsX24, in exon 4). Most interestingly, our data indicated that the cavity of bullous retinoschisis contained a number of fiber-like strands as pillar-like structures in the cavity of typical retinoschisis.

5. Patient consent

The Institutional Review Board of the National Center for Child Health and Development and the Jikei University School of Medicine approved the study, which adhered to the tenets of the Declaration of Helsinki.

The mother of the current patient provided written informed consent for the ophthalmic examinations under general anesthesia, for genetic analysis of the baby and herself, and for the publication of this report.

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Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

Conflict of interest

The following authors have no financial disclosures: S.K., S.T., T.Y., T.H., E.M., K.U., Y.T., A.A., S.N., K.K., and N.A.

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