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

Satoshi Katagiri, Shin Tanaka, Tadashi Yokoi, Takaaki Hayashi, Emiko Matsuzaka, Kazuko Ueda, Tomoyo Yoshida-Uemura, Akira Arakawa, Sachiko Nishina, Kazuaki Kadonosono, Noriyuki Azuma

* Department of Ophthalmology and Laboratory for Visual Science, National Center for Child Health and Development, Tokyo, Japan
b Department of Ophthalmology, The Jikei University School of Medicine, Tokyo, Japan
c Department of Ophthalmology, Yokohama City University Medical Center, Yokohama, Japan

ARTICLE INFO
Article history:
Received 30 August 2016
Received in revised form 30 November 2016
Accepted 8 December 2016
Available online 14 December 2016

Keywords:
X-linked retinoschisis
Novel RS1 mutation
Toddler
Japanese
Optical coherence tomography
Electroretinography

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.

© 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

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

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. Even in the same family, the severities of XLRS differ. Although XLRS generally is diagnosed in school-age children due to moderate visual loss, several cases have been reported with severe phenotypes of bullous retinoschisis with and without vitreous hemorrhage in infants.

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.

http://dx.doi.org/10.1016/j.ajoc.2016.12.009
2451-9936/© 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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.
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-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...
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/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.12−14 In the current case, two types of schisis were seen in the SS-OCT images. Although one was INL scihsi with a general appearance, the other was surprisingly characteristic. In the schisis cavity of bullish retinoschisis, a number of hyperreflective fiber-like strands were seen. Because there appeared to be no layers other than the retinal nerve fibers which become 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 bullish retinoschisis 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.5 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 bullish retinoschisis and the identified RS1 mutations differed.7−9 Interestingly, these cases also showed bilateral bullish 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
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.

Funding

This work was supported by grants from the Ministry of Health, Labour and Welfare (H24-Nanchi-Ippan-031), the National Center for Child Health and Development (#25-7), and the Ministry of Education, Culture, Sports, Science, and Technology of Japan (Grant-in-Aid for Scientific Research [C] 25462738).

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.

Acknowledgments

We thank the patient for participating in this study.

References

1. George ND, Yates JR, Moore AT. X linked retinoschisis. Br J Ophthalmol. 1995;79:697–702.
2. George ND, Yates JR, Moore AT. Clinical features in affected males with X-linked retinoschisis. Archives Ophthalmol. 1996;114:274–280.
3. Sauer CG, Gehrig A, Warneke-Wittstock R, et al. Positional cloning of the gene associated with X-linked juvenile retinoschisis. Nat Genet. 1997;17:164–170.
4. Eksandh LC, Ponjavic V, Ayyagari R, et al. Phenotypic expression of juvenile X-linked retinoschisis in Swedish families with different mutations in the XLRS1 gene. Archives Ophthalmol. 2000;118:1098–1104.
5. Shinoda K, Ishida S, Oguchi Y, Mashima Y. Clinical characteristics of 14 Japanese patients with X-linked juvenile retinoschisis associated with XLRS1 mutation. Ophthalmic Genet. 2000;21:171–180.
6. Molday RS, Kellner U, Weber BH. X-linked juvenile retinoschisis: clinical diagnosis, genetic analysis, and molecular mechanisms. Prog Retin Eye Res. 2012;31:195–212.
7. Prasad A, Wagner R, Bhagat N. Vitreous hemorrhage as the initial manifestation of X-linked retinoschisis in a 9-month-old infant. J Pediatr Ophthalmol strabismus. 2006;43:56–58.
8. Renner AB, Kellner U, Fiebig B, Cropp E, Foerster MH, Weber BH. ERG variability in X-linked congenital retinoschisis patients with mutations in the RS1 gene and the diagnostic importance of fundus autofluorescence and OCT. Documenta Ophthalmol Adv Ophthalmol. 2008;116:97–109.
9. Lee JJ, Kim JH, Kim SY, Park SS, Yu YS. Infantile vitreous hemorrhage as the initial presentation of X-linked juvenile retinoschisis. Korean J Ophthalmol KJO. 2009;23:118–120.
10. McCulloch DL, Marmor MF, Briggell MG, et al. ISCEV Standard for full-field clinical electrotoretinography (2015 update). Documenta Ophthalmol Adv Ophthalmol. 2015;130:1–12.
11. Yokoi T, Nishina S, Fukami M, et al. Genotype–phenotype correlation of PAX6 gene mutations in aniridia. Hum Genome Var. 2016;3:15052.
12. Hayashi T, Omoto S, Takeuchi T, Kozaki K, Ueoka Y, Kitahara K. Four Japanese male patients with juvenile retinoschisis: only three have mutations in the RS1 gene. Am J Ophthalmol. 2004;138:788–798.
13. Gerth C, Zawadzki RJ, Werner JS, Heon E. Retinal morphological changes of patients with X-linked retinoschisis evaluated by Fourier-domain optical coherence tomography. Archives Ophthalmol. 2008;126:807–811.
14. Gregori NZ, Berrocal AM, Gregori G, et al. Macular spectral-domain optical coherence tomography in patients with X linked retinoschisis. Br J Ophthalmol. 2009;93:373–378.
15. Yu J, Ni Y, Keane PA, Jhang C, Wang W, Xu G. Foveomacular schisis in juvenile X-linked retinoschisis: an optical coherence tomography study. Am J Ophthalmol. 2010;149:973–978. e972.