

This article is licensed under the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC) (<http://www.karger.com/Services/OpenAccessLicense>). Usage and distribution for commercial purposes requires written permission.

Case Report

Galactosialidosis Type IIb with Bilateral Macular Cherry-Red Spots but Mild Dysfunction

Hanon Fukuyo^a Yuji Inoue^a Hidenori Takahashi^a Yu Hatano^b
Toko Shibuya^c Norio Sakai^d Hidetoshi Kawashima^a

^aDepartment of Ophthalmology, Jichi Medical University, Tochigi, Japan; ^bDepartment of Family Medicine and Community Health, Duke University, Durham, NC, USA; ^cDepartment of Pediatrics, Osaka University Graduate School of Medicine, Osaka, Japan; ^dChild Healthcare and Genetic Science Laboratory, Division of Health Sciences, Osaka University Graduate School of Medicine, Osaka, Japan

Keywords

Galactosialidosis · CTSA · Cherry-red spots · Lysosomal storage disease

Abstract

Galactosialidosis is a rare metabolic disorder resulting from mutations in the CTSA gene. Few studies have reported on the ocular findings of galactosialidosis type IIb in detail. We report on a case of galactosialidosis, the diagnosis of which was suggested by bilateral macular cherry-red spots, which is an indication of lysosomal storage disease. In this case, retinal and systemic dysfunctions were mild. Genetic studies revealed an abnormality of relevant protective proteins, and thus a definitive diagnosis was made. The patient was a 35-year-old man who had blurred vision from young age, but he did not seek any therapy due to good visual acuity. He visited a local clinic after the blurred vision in the left eye worsened and was referred to us for bilateral macular cherry-red spots. He had no family history of note. We observed fine grayish-white deposits in the corneal stroma and fine opacity of the lens. Optical coherence

tomography showed a hyperreflective region and a thick bilateral retinal ganglion cell layer. Goldmann perimetry showed focal loss of sensitivity. There was almost no functional decline noted on multifocal electroretinography. Lysosomal storage disease was suspected due to corneal clouding and macular cherry-red spots, and so further evaluation was performed. Though neurological abnormality was mild, we made a diagnosis of galactosialidosis because of decreased activity of β -galactosidase and sialidase. Genetic studies revealed an abnormality of relevant protective proteins. Since the onset was later in life and clinical symptoms were mild, we expect that the ophthalmological findings will remain stable. Long-term observation is necessary for this case.

© 2020 The Author(s)
Published by S. Karger AG, Basel

Introduction

Galactosialidosis is a rare metabolic disorder resulting from mutations in the CTSA gene, which encodes a protective protein; this mutation leads to deficiency in lysosomal sialidase and beta-galactosidase [1, 2]. The ocular manifestations of this disease include corneal opacity and macular cherry-red spots, as well as lenticular opacity [1, 3]. In our case, the patient was suspected to have a lysosomal storage disorder based on bilateral corneal opacity and cherry-red spots. We identified a homozygous mutation in the CTSA gene – IVS7 + 3A>G – and made a definitive diagnosis of galactosialidosis. This mutation has been reported in late onset galactosialidosis, but few studies have reported the ocular findings in detail.

Case Presentation

A 35-year-old man was aware of having bilateral blurred vision from young age, but had not consulted an ophthalmologist. He was found to have bilateral corneal opacity in January 2016 while being examined for prescription glasses at Clinic A. He was referred to Hospital B in May 2016, where examinations raised a suspicion of corneal dystrophy; however, he had good visual acuity and no treatment was prescribed. He underwent examination again at Hospital B for deterioration of the blurred vision in his left eye in July 2017, and cherry-red spots were detected. He showed no improvement on follow-up examination, and was referred to our hospital in September 2017.

The patient's past medical history was unremarkable, and his parents are not related. His parents have no visual problems and are in good health as of this writing.

The following findings were noted at the initial examination. Best-corrected visual acuity (BCVA) was 6/5 in the right eye and 6/7.5 in the left eye. Ocular pressure was within the normal range at 15 mm Hg in the right eye and 18 mm Hg in the left eye. Fine, grayish-white opacities were observed bilaterally across the entire corneal stroma, but no signs of inflammation in the anterior chamber were observed on slit-lamp biomicroscopy. Fine opacities were observed centrally on the posterior cortex of the lens as optical media findings (Fig. 1a–d). Cherry-red spots were observed in the fundi bilaterally (Fig. 1e, f). Swept-source optical coherence tomography (SS-OCT) (Triton plus; Topcon Corporation, Tokyo, Japan) revealed a thickened and hyperreflective retinal ganglion cell layer (Fig. 1g, h). The OCT scans also

revealed partial slight elevation of the retinal pigment epithelium in the right eye and a small amount of temporal subretinal fluid in the left eye. Fundus autofluorescence imaging using the Heidelberg retina angiograph 2 (HRA2) (Heidelberg Engineering GmbH, Heidelberg, Germany) revealed hyperfluorescence in the range of a 1.5-mm optic disc diameter around the fovea bilaterally as in a previous report [4]. Fluorescein angiography using HRA2 revealed no clear abnormalities. Goldmann visual field perimetry showed bilaterally decreased central sensitivity (Fig. 2). The Humphrey visual field test with the central 24–2 SITA-Standard program using the Humphrey Field Analyzer (Carl Zeiss Meditec AG, Jena, Germany) revealed slightly decreased overall sensitivity bilaterally. Multifocal electroretinography (ERG) (LE-4000; Tomay Corporation, Nagoya, Japan) using a 37-hexagon stimulus array was performed according to the protocols of the International Society for Clinical Electrophysiology of Vision [5] and was largely normal for both eyes, although the central responses showed slight attenuation for normal eyes (Fig. 3).

A lysosomal storage disorder was suspected based on the cherry-red spots and opacity in the cornea, and the patient underwent a detailed systemic examination. This examination revealed very mild gargoylism, exaggerated tendon reflexes bilaterally, and tandem gait suggestive of cerebellar ataxia. Hasegawa's Dementia Scale assessment yielded a normal result – 30/30. The patient had no seizures or myoclonus. Blood analyses revealed lymphocyte vacuolation. Peripheral nerve conduction testing disclosed latency. Blood enzyme-activity analyses revealed low beta-galactosidase and sialidase levels. Skin biopsy showed decreased activity for both these lysosomal enzymes in dermal fibroblasts. Therefore, the patient was diagnosed as having galactosialidosis.

After obtaining informed consent, genomic DNA was prepared from the patient's blood. PCR amplification, for all exons including the exon-intron boundary, and direct sequencing were performed for the CTSA gene as reported previously [6]. The homozygous mutation IVS7 + 3A>G was detected in the CTSA gene on direct sequencing with genomic DNA extracted from blood. Formerly described as SpDEx7, this is the most common splice site mutation in Japanese galactosialidosis patients, and is mostly found in late-onset galactosialidosis [6].

Discussion/Conclusions

Galactosialidosis is a genetic metabolic disorder characterized by deficiency of the lysosomal enzymes sialidase and beta-galactosidase. Goldberg et al. [1] have recently reported on patients with cherry red-spots and beta-galactosidase deficiency, and the disease concept was established in the 1990s.

Sakuraba et al. [7] classified galactosialidosis into three types based on timing of onset and clinical manifestations. Type I is the early infantile form, type II is the juvenile or adult form, and type III is the late infantile form. Type II galactosialidosis is further subdivided into type IIa – a severe condition with a relatively early onset – and type IIb – a minor condition with a late onset. In the case reported here, the condition was mild and was first identified when the patient was an adult; therefore, it was considered type IIb galactosialidosis. Type II manifestations can include myoclonus and other involuntary movements, such as cerebellar ataxia, seizures, pyramidal signs, intellectual disability, ocular manifestations, auditory disorder, gargoylism, and lymphocyte vacuolation. However, the manifestations in this case – mild

cerebellar ataxia, gargoylism, and vacuolated lymphocytes – were limited. Galactosialidosis generally shows autosomal recessive inheritance [8], but in this case, there was no obvious family history of the disease and his parents were not close relatives. Although galactosialidosis is a rare disease, his parents could have harbored the causative IVS7 + 3A>G mutation by chance.

Galactosialidosis has been reported in about 80 cases worldwide, and about 60% of these reports are from Japan [9]. Previously reported cases of galactosialidosis [4, 10–12] are summarized in Table 1. Cherry-red spots were observed in the fundus in all cases. This phenomenon of cherry-red spots is observed with thinning of opacities due to a reduction in ganglion cell density towards the foveolar region and the periphery of the retina, which in turn arises from the greatest turbidity being around the fovea, where ganglion cell density is high, with a characteristic accumulation of lysosomal lipids in retinal ganglion cells. Yamazaki et al. [4] reported that cherry-red spots in the fundus are not clearly apparent at the early stage of the disease, and speculated that fundus autofluorescence imaging might have higher sensitivity. OCT enables visualization of a thickened retinal ganglion cell layer due to the accumulation of metabolites. OCT findings in galactosialidosis have been reported in 1 case [4], and were similar to those seen in our case. Similar OCT findings have also been observed in sialidosis and other forms of lipidosis. Findings on fundus examination and OCT in 2 sialidosis patients followed for 5 years remained almost constant [13]. However, in this case, abnormalities of the outer retina were noted. For unknown reasons, the subretinal fluid disappeared after 1 month, but the function of the outer retina may also be impaired.

The decrease in retinal function is often mild in galactosialidosis patients, although abnormalities appear in the fundus and on OCT. In this case, only mild decreased sensitivity was observed on the Goldmann visual field examination. Also, multifocal ERG did not show any obvious abnormality except for the central responses, which showed slight attenuation. Histopathological examination revealed accumulation of phospholipids, proteinaceous material, and a lipofuscin-like substance in the ganglion cells and amacrine cells of the retina [14]. The results of multifocal ERG and visual field examination indicated mild photoreceptor dysfunction, although with obvious ganglion cell dysfunction.

In the right eye OCT, RPE was partially elevated. The cause is unknown. In both eyes, the choroid was thick, the blood vessels in the choroid were dilated. The pressure in the choroid might be increased. Central serous chorioretinopathy (CSC) prevalence is high in Japan and small PEDs appear in CSC. The elevated RPE may have the same pathology as CSC. However, at the moment of fluorescein angiography leak points were not present, and thus it was not considered as an active CSC. It may not be directly related to the pathology of galactosialidosis.

Corneal opacity is generally recognized as fine opacities in the central and deeper layers of the stroma in adults; however, in this case, fine grayish-white opacities were similarly observed over the entire corneal stroma bilaterally. The cause of the corneal opacity remains to be elucidated.

Galactosialidosis is caused by deficiency in cathepsin A. This protein is encoded by the CTSA gene and has a strong protective function for beta-galactosidase stabilization and sialidase activity. A previous report showed type IIb patients with a homozygous spliced SpDEx7 mutation [15]; however, details of ocular complications were not reported. In this case, the patient also has this splice mutation in the homozygous condition. To our knowledge, ours is the first report to describe this ocular phenotype in detail.

Currently, there is no effective treatment for galactosialidosis, and management is only symptomatic. However, type IIb galactosialidosis patients are reported to show little deterioration in visual acuity during 10-year follow-up examinations [11]. Considering the lack of systemic symptoms and the long delay in diagnosis, minimal deterioration in visual acuity is predicted for this patient; however, the clinical course needs to be monitored over the long term.

Statement of Ethics

This study was conducted according to the guidelines for human studies and was carried out ethically in accordance with the World Medical Association Declaration of Helsinki. The patient provided informed consent for this case to be published. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board of Jichi Medical University Hospital (reference number 17-100).

Disclosure Statement

Hanon Fukuyo, Yu Hatano, Toko Shibuya, and Norio Sakai have no conflicts of interests to declare. Yuji Inoue received lecturer's fees from Alcon Pharmaceuticals, Bayer Yakuhin, Novartis Pharmaceuticals, Santen Pharmaceuticals, and Senju Pharmaceutical Co., unrelated to this report. Hidenori Takahashi received grants from Alcon Pharmaceuticals, Bayer Yakuhin, and Senju Pharmaceutical Co., consultant's fees from Novartis Pharmaceuticals, and lecturer's fees from Alcon Pharmaceuticals, Bayer Yakuhin, Kowa Pharmaceutical Co., Novartis Pharmaceuticals, Pfizer, Santen Pharmaceuticals, and Senju Pharmaceutical Co., unrelated to this report. Hidenori Takahashi has a pending patent and is a co-founder of DeepEye Vision LLC. Hidetoshi Kawashima received grants from Heiwa Iyou Shokai Co., Hoya Corporation, Linical Co., Ltd., Santen Pharmaceuticals, and Senju Pharmaceuticals, consultant's fees from Heiwa Iyou Shokai Co., and Hoya Corporation, and lecturer's fees from Alcon Pharmaceuticals, Kowa Pharmaceutical Co., Mitsubishi Tanabe Pharma, Novartis Pharmaceuticals, Otsuka Pharmaceutical Co., Santen Pharmaceuticals, and Senju Pharmaceutical Co., unrelated to this report.

Funding Sources

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contributions

H.F. was responsible for obtaining consent and collecting data. Y.I. was responsible for drafting the manuscript. H.T. was responsible for analysis and interpretation of the data. Y.H. contributed to systemic examination and medical description. T.S. and N.S. were responsible

for genetic analysis, interpretation, and writing the genetics aspects of the manuscript. H.K. designed the overall concept and revised the draft. All authors approved the final version.

References

- 1 Goldberg MF, Cotlier E, Fichenscher LG, Kenyon K, Enat R, Borowsky SA. Macular cherry-red spot, corneal clouding, and β -galactosialidase deficiency. *Arch Intern Med*. 1971;128(3):387–98.
- 2 Lowden JA, O'Brien JS. Sialidosis: a review of human neuraminidase deficiency. *Am J Hum Genet*. 1979 Jan;31(1):1–18.
- 3 Usui T, Takagi M, Abe H, Iwata K, Tsuji S, Miyatake T. Adult-form galactosialidosis: ocular findings in three cases. *Ophthalmologica*. 1991;203(4):176–9.
- 4 Yamazaki R, Tsunoda K, Fujinami K, Noda T, Tsubota K. Fundus autofluorescence imaging in a patient with the juvenile form of galactosialidosis. *Ophthalmic Surg Lasers Imaging Retina*. 2014 May-Jun;45(3):259–61.
- 5 Hood DC, Bach M, Brigell M, Keating D, Kondo M, Lyons JS, et al.; International Society For Clinical Electrophysiology of Vision. ISCEV standard for clinical multifocal electroretinography (mfERG) (2011 edition). *Doc Ophthalmol*. 2012 Feb;124(1):1–13.
- 6 Shimmoto M, Fukuhara Y, Itoh K, Oshima A, Sakuraba H, Suzuki Y. Protective protein gene mutations in galactosialidosis. *J Clin Invest*. 1993 Jun;91(6):2393–8.
- 7 Sakuraba H, Itoh K, Shimmoto M. [Multifunctional protective protein and its genetic deficiency 'galactosialidosis']. *Seikagaku*. 1993 Jul;65(7):561–6. Japanese.
- 8 D'Azzo A, Hoogeveen A, Reuser AJ, Robinson D, Galjaard H. Molecular defect in combined beta-galactosidase and neuraminidase deficiency in man. *Proc Natl Acad Sci USA*. 1982 Aug;79(15):4535–9.
- 9 Hossain MA, Higaki K, Shinpo M, Nanba E, Suzuki Y, Ozono K, et al. Chemical chaperone treatment for galactosialidosis: effect of NOEV on β -galactosidase activities in fibroblasts. *Brain Dev*. 2016 Feb;38(2):175–80.
- 10 Tanabe S, Tabuchi Y, Hirano J, Murakami M. A case of galactosialidosis. *Rinsho Ganka*. 1987;41:824–5. Japanese.
- 11 Kiuchi T, Sekine Y, Usuki Y, et al. Longterm clinical course of galactosialidosis in two adult male siblings. *Rinsho Ganka*. 1996;50:173–7. Japanese.
- 12 Tsujino N, Tagawa Y. Two cases of galactosialidosis. *Rinsho Ganka*. 1997;51:462–6. Japanese.
- 13 Rosenberg R, Halimi E, Mention-Mulliez K, Cuisset JM, Holder M, Defoort-Dhellemmes S. Five year follow-up of two sisters with type II sialidosis: systemic and ophthalmic findings including OCT analysis. *J Pediatr Ophthalmol Strabismus*. 2013 Jul;50 Online:e33–6.
- 14 Usui T, Sawaguchi S, Abe H, Iwata K, Oyanagi K. Late-infantile type galactosialidosis. Histopathology of the retina and optic nerve. *Arch Ophthalmol*. 1991 Apr;109(4):542–6.
- 15 Shimmoto M, Takano T, Fukuhara Y, Oshima A, Sakuraba H, Suzuki Y. Japanese-type adult galactosialidosis. A unique and common splice junction mutation causing exon skipping in the protective protein/carboxypeptidase gene. *Proc Jpn Acad*. 1990;66B(10):217–22.

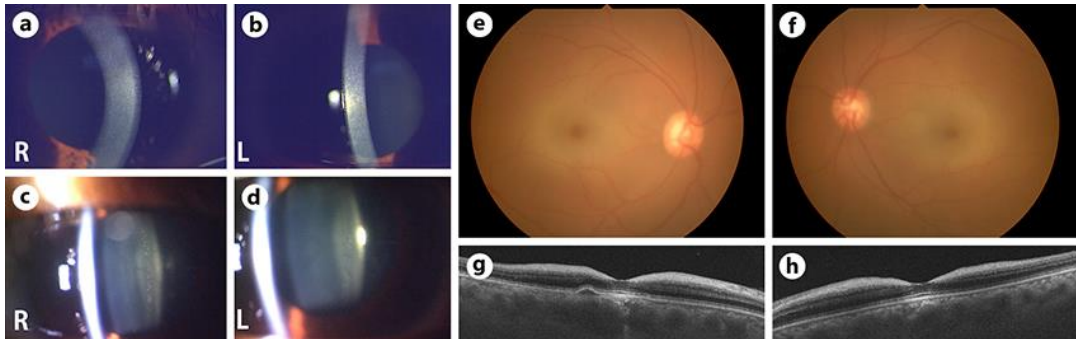


Fig. 1. Anterior segment of the eye (a–d). Fine opacities in the corneal stroma, bilateral (a right eye; b left eye). Fine opacities in the center of the posterior capsule of the lens (c right eye; d left eye). Fundus photography (e right eye; f left eye). Macular cherry-red spots, bilaterally. Horizontal section of OCT. Hyperreflective and thickened retinal ganglion cell layer, bilaterally (g right eye; h left eye). Partial slight elevation of the retinal pigment epithelium in the right eye (g), and a small amount of temporal subretinal fluid in the left eye (h).

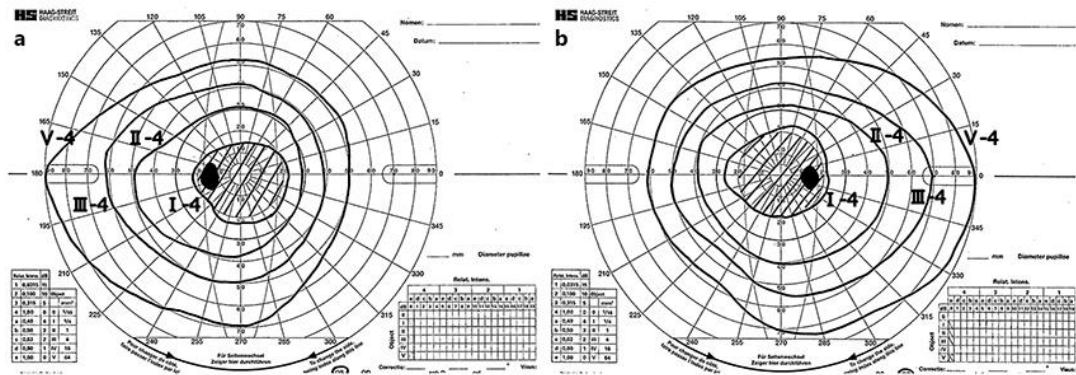


Fig. 2. Goldmann perimetry (a left eye; b right eye). Decrease in central sensitivity with no stable reaction on the diagonal line. No abnormality is found in the peripheral visual field in both eyes.

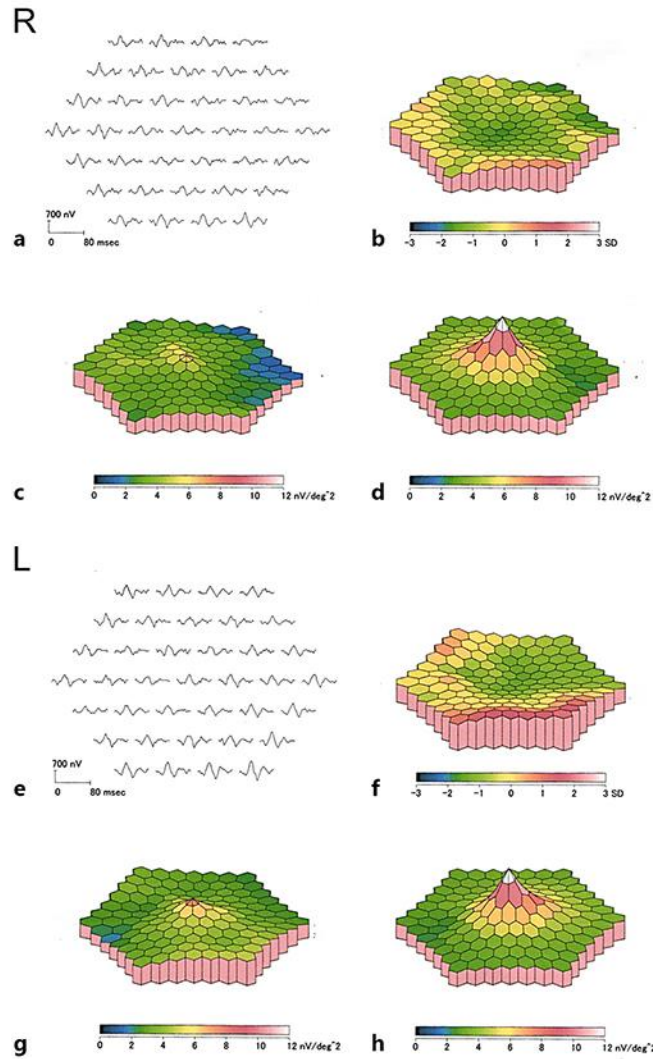


Fig. 3. Multifocal ERG using a 37-hexagon stimulus array. The central responses show slight attenuation for normal eyes, but there is almost no functional decline. Upper panel: right eye. Lower panel: left eye. Trace array showing all local responses in the patient (**a, e**). Three-dimensional topographic map of the deviation of the patient for normal eyes (**b, f**), the map of the patient (**c, g**), and average for normal eyes (**d, h**).

Table 1. Previously reported cases of galactosialidosis

Author	Age/ sex	Close relatives	Family his- tory	1st exam BCVA	Corneal opacity	Lenticular opacity	Cherry-red spots	Field of vision
Tanabe et al. [10]	36 F	+	-	R: 6/300 L: 6/600	+	N/A	+	N/A
Kiuchi et al. [11]	34 M	-	+*	R: HM L: HM	+	N/A	+	N/A
	30 M	-	+*	R: 6/9.5 L: 6/12	+	N/A	+	†, ‡
Tsujino et al. [12]	36 M	+	-	R: 6/15 L: 6/9.5	+	+	+	†, §
	21 M	-	-	R: 6/6 L: 6/7.5	+	+	+	†
Yamazaki et al. [4]	19 M	-	-	R: 6/19 L: 6/19	-	N/A	+	§

N/A, not recorded. * Siblings. † Enlargement of the blind spot of Mariotte. ‡ Depression of isopter. § Central scotoma.