A Case of Fabry Disease with Central Retinal Artery Occlusion

Daisuke Nakata\textsuperscript{a, b}, Hiroshi Okada\textsuperscript{a}, Yoshiaki Shimada\textsuperscript{b}, Atsuhiro Tanikawa\textsuperscript{b}, Masayuki Horiguchi\textsuperscript{b}, Yasuki Ito\textsuperscript{b}

\textsuperscript{a}Department of Ophthalmology, Toyokawa City Hospital, Toyokawa, Japan; \textsuperscript{b}Department of Ophthalmology, School of Medicine, Fujita Health University, Toyoake, Japan

Keywords
Central retinal artery occlusion \cdot Cornea verticillata \cdot Fabry disease

Abstract
We report a case of Fabry disease diagnosed after recurrent cerebral infarction in a patient with central retinal artery occlusion (CRAO). A 23-year-old man presented with vision loss in his right eye (20/2000), showing CRAO. There was no identified cause for the loss of vision; however, corneal verticillata was detected in both eyes on the recurrence of the cerebral infarction. The $\alpha$-galactosidase activity in leukocytes was significantly reduced to $<0.3$ nmol/mg of protein/hour, leading to a definitive diagnosis of Fabry disease. Enzyme replacement therapy was commenced concomitant to rehabilitation. It is necessary to identify Fabry disease as a cause of CRAO in young individuals, and the detection of cornea verticillata, used frequently as an ocular finding, is helpful.

Introduction
Fabry disease is an inborn error of lipid metabolism caused by a congenital deficiency of the gene for the lysosomal enzyme $\alpha$-galactosidase A (GLA) [1, 2]. Glycolipids, the substrates of GLA, accumulate in the lysosomes of various cells, including the vascular endothelial cells, and cause various clinical symptoms in each organ, centering primarily on the kidney and the heart. Central retinal artery occlusion (CRAO) occurs more frequently in the elderly with systemic diseases such as hypertension, arteriosclerosis, and cardiovascular diseases, including...
arrhythmia and valvular heart disease [3]. We report a case of Fabry disease diagnosed due to recurrent cerebral infarction in a patient with CRAO.

Case Report

A 23-year-old man visited the Department of Ophthalmology, Toyokawa City Hospital, on April 15, 2019, for evaluation of visual loss in the right eye. He noticed a sudden decrease in visual acuity in his right eye 4–5 days before the consultation. The medical history was generally unremarkable.

Clinical examination revealed his left eye to be normal; however, the right eye showed cherry-red spots, as shown in Figure 1 and loss of visual acuity (20/2000). The patient was diagnosed with CRAO and urgently hospitalized on the same day.

An eye massage was performed on the right eye, and an intravenous drip infusion was administered for approximately 1 week while gradually reducing the thrombolytic drug urokinase by 240,000 units/day. We searched for the cause of CRAO but found no arrhythmias, heart disease, collagen disease, or vasculitis. Carotid echocardiogram and magnetic resonance imaging revealed no carotid artery stenosis. Since he was moderately obese with a body mass index of 30.85, he was encouraged to improve his lifestyle and pay close attention to his diet, exercise, and dehydration.

Unfortunately, the patient did not respond to the initial therapy; his visual acuity remained unchanged, and he developed optic nerve atrophy. He suffered from dizziness since August 2019, and cerebral infarction on the right side of the pons was detected. He was prescribed 80 mg of ozagrel sodium, 100 mg of aspirin, and 75 mg of clopidogrel orally following atherothrombotic cerebral infarction. The cause was scrutinized again with no notable findings. Furthermore, the patient relocated because of employment and left our hospital in February 2020 and returned in February 2021.

In April 2021, he was transported to the hospital as an emergency case due to the paralysis of the right upper limb and was admitted immediately after a recurrence of cerebral infarction in the left thalamus. The patient underwent an ophthalmologic evaluation, and a slit lamp microscopic examination revealed cornea verticillata in both eyes, as shown in Figure 2. Since the recurrent cerebral infarction occurred at a young age, we performed another systemic examination and found that the GLA activity in leukocytes was markedly decreased to

Fig. 1. Fundus image at the first consultation. a Right eye showing CRAO. b Left eye.
<0.3 nmol/mg of protein/hour (reference value, 49.8–116.4), leading to a definitive diagnosis of Fabry disease. In addition, GLA gene analysis revealed an exon 7 c.1024 C>T (p.R342X) nonsense variant in the hemi-conjugated body. This mutation has been reported by Davies et al. [4] as a case of classical Fabry disease. Currently, infusion therapy of agalsidase beta 70 mg (1.0 mg/kg) is administered every other week as enzyme replacement therapy concurrently with rehabilitation.

Discussion

Sher et al. [5] and Andersen et al. [6] have reported CRAO due to Fabry disease. Although it seems to be a rare cause, Fledelius et al. [7] reported that patients with Fabry disease developed CRAO in two out of 39 patients (5.1%) during a 10-year follow-up. According to Degraba et al. [8], neutrophils and vascular endothelial cells are activated in Fabry disease and form a thrombus. In a study by Utsumi et al. [9], thrombosis was observed in 10 out of 65 cases (15%) of Fabry disease. The frequency of central nervous system complications was not low. In the current case, it was considered that CRAO developed due to dehydration that occurred daily during the busy period of movement as part of the part-time work in the transportation industry at the time of the first ophthalmology examination. There were no notable findings in the full body examination, and lifestyle guidance such as reduction of weight and diligent hydration was provided. A few months later, cerebral infarction developed, and it was speculated that in Fabry disease, insufficient regulation of sweating [1] and thrombotic tendency [8, 9] also worsened retinal circulation, leading to CRAO. Although enzyme replacement therapy is used as a treatment method, Fabry disease is a chronic progressive disease. According to Germain et al. [10], its effectiveness is high in the early stage of onset and declines in the terminal stage. Thus, early diagnosis and intervention affect the prognosis. According to Waldek et al. [11], the life expectancy of males with Fabry disease was 58.2 years, compared with 74.7 years in the general population of the USA, while the life expectancy of females was 75.4 years, compared with 80.0 in the general population. The most common cause of death among both genders was cardiovascular disease. Beck et al. [12] reported that replacement therapy also appeared to delay the onset of morbidity and mortality. Early detection and treatment of as many patients with Fabry disease as possible in collaboration with internal medicine is important.

Fig. 2. Slit-lamp at the May 2021 re-examination. Cornea verticillata is seen in both eyes.

It is necessary to search for the cause of CRAO developing at a young age while considering Fabry disease. In such cases, it is crucial to carefully observe the cornea as the presence or absence of cornea verticillata, used frequently as an ocular finding, is helpful.
Acknowledgment

We would like to thank Editage (www.editage.com) for English language editing.

Statement of Ethics

This case report was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study protocol was reviewed, and the need for approval was waived by the Ethics Committee of the Toyokawa City Hospital. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors declare that they did not receive any funding for this study.

Author Contributions

Daisuke Nakata and Hiroshi Okada examined the patient and collected clinical data. Daisuke Nakata drafted the manuscript. Atsuhiro Tanikawa and Yoshiaki Shimada performed manuscript editing. Masayuki Horiguchi and Yasuki Ito reviewed the manuscript. All authors read and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 El-Abassi R, Singhal D, England JD. Fabry’s disease. J Neurol Sci. 2014;344(1–2):5–19.
2 Sodi A, Ioannidis AS, Mehta A, Davey C, Beck M, Pitz S. Ocular manifestations of Fabry’s disease: data from the Fabry outcome survey. Br J Ophthalmol. 2007;91(2):210–4.
3 Brown GC, Magargal LE, Shields JA, Goldberg RE, Walsh PN. Retinal arterial obstruction in children and young adults. Ophthalmology. 1981;88(1):18–25.
4 Davies JP, Winchester BG, Malcolm S. Mutation analysis in patients with the typical form of Anderson-Fabry disease. Hum Mol Genet. 1993;2(7):1051–3.
5 Sher NA, Reiff W, Letson RD, Desnick RJ. Central retinal artery occlusion complicating Fabry’s disease. Arch Ophthalmol. 1978;96(5):815–7.
6 Andersen MV, Dahl H, Fledelius H, Nielsen NV. Central retinal artery occlusion in a patient with Fabry’s disease documented by scanning laser ophthalmoscopy. Acta Ophthalmol. 1994;72(5):635–8.
7 Fledelius HC, Sandfeld L, Rasmussen ÅK, Madsen CV, Feldt-Rasmussen U. Ophthalmic experience over 10 years in an observational nationwide Danish cohort of Fabry patients with access to enzyme replacement. Acta Ophthalmol. 2015;93(3):258–64.
8 DeGraba T, Azhar S, Dignat-George F, Brown E, Boutière B, Altarescu G, et al. Profile of endothelial and leukocyte activation in Fabry patients. Ann Neurol. 2000;47(2):229–33.
9 Utsumi K, Ueda K, Watanabe M, Sakamaki M, Arii K, Yamazaki M, et al. Thrombosis in Japanese patients with Fabry disease. J Neurol Sci. 2009;283(1–2):83–5.
10 Germain DP, Charrow J, Desnick RJ, Guffon N, Kempf J, Lachmann RH, et al. Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease. J Med Genet. 2015;52(5):353–8.
11 Waldek S, Patel MR, Banikazemi M, Lemay R, Lee P. Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry registry. Genet Med. 2009 Nov;11(11):790–6.
12 Beck M, Hughes D, Kampmann C, Larroque S, Mehta A, Pintos-Morell G, et al. Long-term effectiveness of agalsidase alfa enzyme replacement in Fabry disease: a Fabry outcome survey analysis. Mol Genet Metab Rep. 2015 Mar 5;3:21–7.