CASE REPORT

Retinal Ganglion Cell Loss in X-linked Adrenoleukodystrophy with an *ABCD1* Mutation (Gly266Arg)

Yasuhiro Ohkuma¹, Takaaki Hayashi¹, Syouyou Yoshimine¹, Hiroshi Tsuneoka¹, Yoko Terao², Masaharu Akiyama², Hiroyuki Ida², Toya Ohashi², Akihisa Okumura³, Nobuyuki Ebihara⁴, Akira Murakami⁴, and Nobuyuki Shimoza⁵

¹Department of Ophthalmology and ²Department of Pediatrics, The Jikei University School of Medicine, Tokyo, Japan, ³Department of Pediatrics and ⁴Department of Ophthalmology, Juntendo University School of Medicine, Tokyo, Japan, and ⁵Division of Genomics Research, Life Science Research Center, Gifu University, Yanagido, Japan

ABSTRACT

The authors here report a single case of a 10-year-old male patient who presented with severe vision loss associated with progressive demyelination. The patient was diagnosed with X-linked childhood cerebral adrenoleukodystrophy (ALD). Genetic analysis demonstrated a missense mutation (Gly266Arg) in exon 1 of the *ABCD1* gene. His corrected visual acuity confirmed the absolute lack of light perception in both eyes. Funduscopy revealed severe pallor of the optic disc in both eyes. Spectral-domain optical coherence tomography showed thinning of the retinal ganglion cell and inner plexiform layers (GCL and IPL). Thinning of the GCL and IPL may be due to transneuronal retrograde degeneration of ganglion cells secondary to optic tract demyelination.

Keywords: *ABCD1* mutation, adrenoleukodystrophy, ganglion cell layer, optical coherence tomography, retrograde degeneration

INTRODUCTION

Adrenoleukodystrophy (ALD) is a neurodegenerative disease characterised by demyelination of the central nervous system, adrenocortical insufficiency, and the accumulation of very-long-chain fatty acids (VLCFAs) in all tissues.¹ This accumulation results from defective peroxisomal β -oxidation due to various loss-of-function mutations in the *ABCD1* gene on chromosome Xq28.² Among the many clinical ALD phenotypes, the two most frequent are the adult-onset adrenomyeloneuropathy (AMN) characterised by spastic paraparesis and sphincter dysfunction, which develops in the second to fifth decades, and the childhood cerebral form, which has an onset between

6 and 12 years of age. The childhood cerebral form is the most severe clinically and makes up to 40% of ALD phenotypes. Children may present with school difficulties related to attention deficits and may experience behavioural changes caused by visuo-spatial deficits, and hearing symptoms. In addition, up to 90% may have hypoglycaemic and/or salt-losing episodes related to adrenal insufficiency.^{3–5} Among initial symptoms, visual symptoms are seen in about 24% of patients with childhood cerebral ALD.⁶ Progressive visual disturbances occur within next 6 months after the onset of the initial symptoms.⁶ Here we report ocular findings from a patient of childhood cerebral ALD with an *ABCD1* mutation (G266R) in exon 1.

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Correspondence: Yasuhiro Ohkuma, MD, Department of Ophthalmology, The Jikei University School of Medicine, 3-25-8 Nishi-shimbashi, Minato-ku, Tokyo 105-8461, Japan. E-mail: yookuma1110@gmail.com

CASE REPORT

A 10-year-old Japanese male patient visited the Department of Pediatrics at Juntendo University Faculty of Medicine because of a history of intellectual and visual disturbances for over 3 months. His family history was negative for any visual disturbances. His best-corrected logMAR visual acuity (BCVA) was -0.1 in both eyes, with intermittent exotropia. Funduscopy revealed slight bilateral optic disc pallor. Within the next 2 months, his BCVA had decreased to 1.3 (right eye) and 1.1 (left eye). We evaluated fluid-attenuated inversion recovery (FLAIR) and post-gadolinium T1-weighted magnetic resonance imaging (MRI) images at the same scan position. The FLAIR image showed hyperintensity (demyelination) of the white matter around each posterior horn of lateral ventricle. Prominent rim enhancement was observed after intravenous administration of gadolinium, suggesting active areas of demyelination (Figure 1). Goldmann perimetry showed only small islands of vision remaining in the paracentral right visual fields of both eyes, when tested with V4e stimulus (Figure 2). Plasma VLCFA levels in the patient indicated increased VLCFA ratios ($C24:0/C22:0=1.89$, the mean and standard deviation of controls were 1.05 ± 0.16 ; $C26:0/C22:0=0.044$, the mean and standard deviation of controls were 0.012 ± 0.005), whereas plasma VLCFA levels in his unaffected mother showed normal VLCFA ratios ($C24:0/C22:0=0.86$ and $C26:0/C22:0=0.008$). Mutation screening of the *ABCD1* gene was performed using Sanger sequencing, revealing a substituted nucleotide (c.796G→A)

in exon 1, which results in a missense mutation (Gly266Arg) (Figure 3). However, his mother did not have the Gly266Arg mutation (Figure 3). Collectively, childhood cerebral ALD with the de novo mutation (Gly266Arg) was diagnosed, and the patient was referred to undergo bone marrow transplantation (BMT).

At the patient's first visit to the Department of Ophthalmology of The Jikei University School of Medicine (3 months after his initial examination), BCVA revealed absolute lack of light perception in both eyes. Funduscopy revealed no inflammatory cells in the anterior segment or vitreous in either eye; severe pallor of the optic disc was present bilaterally (Figure 4).

Spectral-domain optical coherence tomography (OCT; Cirrus HD-OCT; Carl Zeiss Meditec AG, Dublin, CA, USA) of his left eye was performed by using the high-definition 5-line raster scan protocol (horizontal scan of 6 mm). Appropriate images of the right eye were not obtained because of eye fixation problems. The OCT image in the left eye showed a continuous photoreceptor inner segment/outer segment junction (IS/OS) line throughout the entire region (Figure 5). Two independent observers measured total thicknesses of the retinal ganglion cell layer (GCL) and the inner plexiform layer (IPL) at both 1490 and 1500 μm nasal from the foveal centre and then the two values were averaged to obtain the mean nasal value. Also, total thicknesses of the GCL and IPL were measured at both 1490 and 1500 μm temporal from the foveal centre, and the two values were averaged to obtain the mean temporal value.

FIGURE 1 Fluid-attenuated inversion recovery (FLAIR) and post-gadolinium T1-weighted MRI images at the same scan position. The FLAIR image (A) shows hyperintensity (demyelination) of the white matter around each posterior horn of lateral ventricle. Prominent rim enhancement (arrow) is observed after intravenous administration of gadolinium (B), suggesting active areas of demyelination.

FIGURE 2 Goldmann perimetry shows only small islands of vision remaining in the paracentral right visual fields of both eyes, when tested with V4e stimulus.

FIGURE 3 Nucleotide sequences (exon 1 of the *ABCD1* gene) of the patient and his unaffected mother. The arrow in the patient indicates the position of the substituted nucleotide (c.796G→A), which results in a missense mutation (Gly266Arg).

The mean thickness of our patient was 80.0 μm nasally and 74.5 μm temporally, respectively. The patient's values were compared with previously reported measurements obtained by using spectral-domain Cirrus HD-OCT, demonstrating that the patient's values were markedly thinner than those of age-matched controls.⁷

Regrettably, BMT failed to restore any vision, and the patient continues to have no light perception in either eye.

DISCUSSION

Frequent clinical ophthalmologic findings in childhood ALD are optic atrophy with visual acuity and field losses, strabismus, and other disturbances of ocular motility.⁸ Once visual loss starts, it tends to progress rapidly and lead to severe vision loss. Demyelination of the central visual tracts is generally considered responsible for the vision loss.^{9,10} This demyelination has been hypothesised to be caused by the accumulation of VLCFAs in individuals with ALD, which contributes to demyelination and the promulgation of inflammatory factors related to the pathogenesis of optic nerve dysfunction.¹¹ Histopathology of eyes with ALD reveals loss of ganglion cell and nerve fibre layers and gliosis of the inner retina.^{9,10}

OCT has been used to document differences of the GCL + IPL thickness between amblyopic and unaffected contralateral eyes (the mean age of the patients was 9 years); the mean nasal GCL + IPL thickness was $90.88 \pm 15.79 \mu\text{m}$ in amblyopic eyes and

FIGURE 4 Fundus photography revealed severe pallor of both optic discs.

FIGURE 5 Horizontal scan images of spectral-domain optical coherence tomography (OCT) of the ALD patient (A) and control image of a healthy 9-year-old boy whose best-corrected logMAR visual acuity was -0.1 (B). The OCT image from our patient (A) shows a continuous photoreceptor inner segment/outer segment junction line throughout the entire region and attenuation of the ganglion cell layer and inner plexiform layer (GCL + IPL; double-headed arrows). GCL + IPL thickness of the ALD case is thinner than that of a control (B).

$101.33 \pm 8.52 \mu\text{m}$ in contralateral eyes, and the mean temporal GCL + IPL thicknesses were $84.24 \pm 1.77 \mu\text{m}$ and $90.56 \pm 1.77 \mu\text{m}$ in amblyopic and contralateral eyes, respectively.⁷ The GCL + IPL thicknesses (approximately $80 \mu\text{m}$ nasally and $74.5 \mu\text{m}$ temporally) of our patient with childhood ALD were clearly thinner than those of the age-matched controls, as previously reported.⁷ A major cause of ganglion cell loss is predicted to be due to inferred transneuronal retrograde degeneration.¹² In optic neuritis, a similar demyelinating disease, Syc et al. describe that retrograde degeneration of GCL + IPL was observed at 3 months after onset.¹³ In their report, the mean thickness of GCL + IPL was $76.4 \pm 6.3 \mu\text{m}$ at base line, $66.3 \pm 10.5 \mu\text{m}$ at 3 months after onset, $67.1 \pm 10.3 \mu\text{m}$ at 6 months after onset.¹³ Grainger et al. report a 48-year-old male patient with AMN, showing thinning of retinal nerve fibre layer (RNFL) in the peripapillary region and total retinal thinning of the macula region using time-domain OCT.¹⁴ In histopathology of eyes with ALD, Wray et al. show that loss of retinal

ganglion cells was most evident in the macular area, suggesting that there may be selective vulnerability of the macular ganglion cells.⁹ Aquino et al. study thickness of RNFL using spectral-domain OCT in presymptomatic ALD eyes and age-matched healthy controls and found no differences in measurements.¹⁵

It is reported that visual loss progressed relentlessly in some boys with ALD even despite successful BMT.¹⁶ Gess et al. report that factors correlated with loss of visual acuity after BMT were poor pretransplant MRI severity score, pretransplant performance intelligence quotient, and the presence of pretransplant parieto-occipital demyelination on MRI, and recommend avoiding BMT for advanced ALD.¹⁷ In our case, BMT had no effect on visual improvement. Therefore, although early BMT before severe ganglion cell loss might have improved visual prognosis, BMT is not expected to reverse deficits already accrued in ALD.

In conclusion, rapid visual deterioration, occurring within the next 6 months after onset of neurological

symptoms, is most likely to be caused by progressive thinning of the GCL and IPL, which may be due to transneuronal retrograde degeneration of the retinal ganglion cells secondary to optic radiation demyelination.

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Note: Figures 3, 4 and 5 of this article are available in colour online at <http://informahealthcare.com/oph>.

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