Molecular Genetics and Metabolism Reports 28 (2021) 100778

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Case Report

Brain-sparing cord blood transplantation for the borderline stage of adrenoleukodystrophy

Yutaro Yada [a], Michiko Torio [a], Yuhki Koga [a,*], Fumiya Yamashita [b], Takuya Ichimura [a,c], Katsuhide Eguchi [a], Masataka Ishimura [a], Yuichi Mushimoto [a], Akio Hiwatashi [d], Momoko Sasazuki [a], Ryutaro Kira [b], Yasunari Sakai [a,*], Shouichi Ohga [a]

[a] Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan
[b] Department of Pediatric Neurology, Fukuoka Children's Hospital, Fukuoka 813-0017, Japan
[c] Department of Pediatrics, Yamaguchi University, Ube 755-8505, Japan
[d] Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan

ARTICLE INFO

Keywords:
Adrenoleukodystrophy
Loes score
Reduced-intensity conditioning
Brain-sparing irradiation
Hematopoietic cell transplantation

ABSTRACT

Background: Adrenoleukodystrophy (ALD) is an X-linked disorder characterized by rapidly progressive deterioration of neurocognitive functions and premature death. In addition to the difficulty in identifying the earliest signs of ALD, treatment-associated exacerbation of neurological symptoms has been an obstacle to achieve successful hematopoietic cell transplantation (HCT) for affected children.

Case report: We report a 9-year-boy with ALD. He presented with impairment in social skills compatible to the diagnosis of autism spectrum disorder from 3 years of age. He showed progressive strabismus, slurred speech and dysmetria at 6 years of age. The head MRI showed symmetrical T2-hyperintense lesions in the occipital white matters with a gadolinium enhancement, which extended to the internal capsules. The Loes score was thus calculated as 13. Very-long-chain-fatty-acids were increased to 1.800 (C24:0/C22:0) and 0.077 (C26:0/C22:0) in leukocytes. Sanger sequencing confirmed the pathogenic variant in *ABCD1* (NM_000033.4:p.Gly512Ser). After multidisciplinary discussions over the treatment options, we performed a cord blood HCT with a reduced intensity conditioning (fludarabine, melphalan and brain-sparing total body irradiation). He was fully recovered with >90% chimerism of donor leukocytes at 55 days after HCT. He experienced three times of generalized seizures after discharge, that has been well controlled for 2 years without other complications or neurocognitive deteriorations.

Conclusion: For patients with ALD on a borderline indication for HCT, brain-sparing irradiation might be an alternative option in reduced intensity conditioning. Careful decision-making process and tailored conditioning are critical for the successful outcome of HCT for children with ALD.

1. Introduction

X-linked adrenoleukodystrophy (ALD, MIM #300100) is the most common peroxisome disorder caused by mutations in *ATP-binding cassette transporter subfamily D1* (*ABCD1*), affecting both sex with an estimated birth incidence of about 1/14,700 [1,2]. The gene defect causes impaired transport of acyl-CoA into peroxisomes for β-oxidation and accumulation of very long-chain saturated fatty acids ≥ C22:0 (VLCFA), leading to the involvement of the cerebrum, adrenal glands, spinal cords and peripheral nerve [1,3]. The inflammatory cerebral demyelination occurs peaking in the ages 3–10 years, and affected children develop a progressive neurocognitive dysfunction more rapidly than adults [4]. More than 35% of males show cerebral symptoms in childhood, whereas the process of disease onset remains elusive. The pilot studies on newborn screening and gene therapy are therefore ongoing [2].

Abbreviations: ALD, Adrenoleukodystrophy; VLCFA, very long-chain saturated fatty acids; HCT, hematopoietic cell transplantation; GVHD, graft failure and graft-versus-host disease; CBT, cord blood transplantation; HLA, human leukocyte antigen; ASD, autism spectrum disorder; HDC, hydrocortisone.

* Corresponding authors at: Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.

E-mail addresses: yuuki-k@pediatr.med.kyushu-u.ac.jp (Y. Koga), ysakai22q13@gmail.com (Y. Sakai).

https://doi.org/10.1016/j.ymgmr.2021.100778
Received 22 May 2021; Received in revised form 17 June 2021; Accepted 17 June 2021

Hematopoietic cell transplantation (HCT) is the life-saving standard intervention for cerebral ALD [1–3]. However, several conditions limit the preventive effect on disease progression. These include graft failure and graft-versus-host disease (GVHD) [3,5–7]. As conditioning-associated risks, brain irradiation exacerbates neurological damage [8]. Brain-sparing irradiation may thus circumvent unfavorable outcomes, but it is challenging to reach a consensus for individuals.

We herein present a boy with ALD at borderline intervention for cord blood transplantation (CBT) after brain-sparing total body irradiation.

2. Methods

2.1. Ethics statement

Written informed consent was obtained from parents for genetic diagnosis, treatments and reporting the content of this manuscript. The decision-making process was carefully monitored and supervised by the board councils of medical ethics and palliative care for children in Kyushu University Hospital (Chaired by Sasazuki, Koga and Ohga). This report is a part of our ethics study on the patient-physician relationship (#28-461, #2020-413).

2.2. Hematopoietic cell transplantation

Reduced-intensity conditioning was applied for HCT in non-cancerous hematopoietic disorders [9]. The treatment regimen consists of intravenously administered fludarabine (30 mg/m^2 for 6 days), melphalan (70 mg/m^2 for 2 days), and brain-sparing total body irradiation at 4 Gy. Tacrolimus and 7–10 mg/m^2 methotrexate infusion (days 1, 3 and 6) were used for GVHD prophylaxis. Engraftment, GVHD, and donor chimerism were assessed conventionally [10]. Human leukocyte antigens (HLA)-matched unrelated donors were available at the Japanese Cord Blood Bank Network (JCBBN).

3. Case presentation

A presently 9-year-old Japanese boy is an only child of healthy, unrelated parents. He was born in the 40th week of gestation with normal birth weight (3152 g), height (53.0 cm) and head circumference (32.8 cm). No asphyxia or other complications were observed during the perinatal period. The growth was normal during infancy, while the motor and cognitive development was unremarkable until 18 months of age. He acquired meaningful words at 18 months and began to compose two-word sentences from 27 months of age. His parents noticed his handicaps in social skills because he showed persistent behaviors, repeated words of others, few eye contacts. He was walking on toes at 18 months of age. Being diagnosed of autism spectrum disorder (ASD), he began to attend a regional service for children with verbal and social handicaps from 5 years of age.

The left strabismus and slurred speech emerged at 6 years of age, that brought this patient to Fukuoka Children's Hospital. Funduscopic examination did not show abnormal findings in the retina and optic nerves. However, he had bilateral spasticity in the lower extremities. The physical and neurological examination disclosed dysmetria when he was extending his arms to the target of interest. There was no nystagmus or involuntary movements. The head magnetic resonance imaging (MRI) revealed symmetrical T2-hyperintense lesions, which extended from the occipital-dominant white matters to the posterior limbs of bilateral internal capsules (Fig. 1A). The margins of the occipital lesions showed a gadolinium-enhanced effect (Supplementary Fig. S1A). The Loes score reached 13

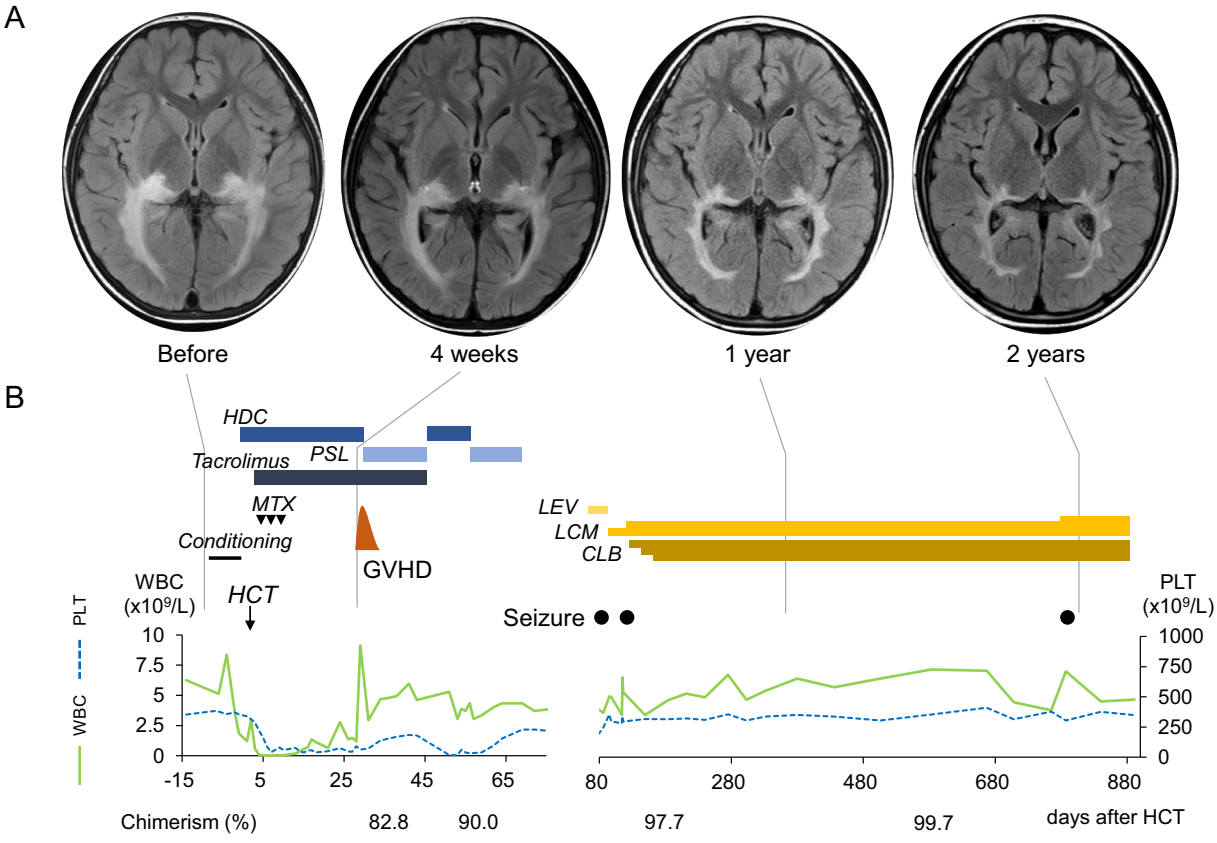

Fig. 1. Clinical and neuroimaging features of the present case. (A) Fluid attenuated inversion recovery images at the initial diagnosis, four weeks, one year and two years after the hematopoietic cell transplantation. Note that demyelinating lesions extended to bilateral internal capsules. (B) Clinical course of hematopoiesis and neurological before and after the hematopoietic cell transplantation. HDC, hydrocortisone; PSL, prednisolone; MTX, methotrexate; LEV, levetiracetam; LCM, lacosamide; CLB, clobazam; GVHD, graft versus host disease; HCT, hematopoietic cell transplantation.

Table 1
Clinical and neuroimaging features of children with X-linked adrenoleukodystrophy before and after umbilical cord blood transplantation.

Case	Age at CBT	HLA compatibility	Number of nucleated; $CD34^+$ cells (/kg)	Conditioning regimen	VLCFA before HCT C24:0/C22:0, C26:0/C22:0	Loes score		NFS		Engrafted (days)	Study period (months)
						Before	After (months)	Before	After		
With involvement of internal capsule											
Kato 8	4	8/8	NA	F + M + 4Gy	2.030, 0.119	13	24 (36)	6	21	21	46
Kato 15	5	6/8	NA	F + M + 4Gy	1.710, 0.076	11	15.5 (7)	2	25	21 (2nd HCT)	20
Kato 16	5	8/8	NA	F + M + 4Gy	1.930, 0.116	20	31 (7)	2	22	19	16
Present Case	6	8/8	5.6×10^7; 1.8×10^5	F + M + 4Gy [Bs]	1.800, 0.077	13	14 (27)	2	3	24	27
Kato 11	10	6/8	NA	F + M + 4Gy	1.429, 0.026	15	16.5 (1)	2	NA	NA	36
Without involvement of internal capsule											
Kato 4	6	6/8	NA	F + M + 3Gy	1.500, 0.054	16	14 (58)	1	3	20 (2nd HCT)	76
Niizuma 1	7	8/8	3.5×10^7; 1.2×10^5	F + M + 4Gy [Bs]	2.010, 0.111	14.5	15 (8)	NA	NA	25	20
Awaya	8	4/6	3.2×10^7; 0.7×10^5	F + M + 4Gy	NA	11.5	13 (36)	NA	NA	16	NA
Kato 1	11	8/8	NA	F + M + 4Gy	1.184, 0.020	14	12 (52)	1	3	19	91
Kato 2	9	6/8	NA	F + M + 4Gy	1.166, 0.018	18	14 (72)	2	8	24	88
Kato 9	9	8/8	NA	F + M + 4Gy	1.690, 0.089	14	14 (26)	2	3	20	45
Kato 10	10	7/8	NA	F + M + 4Gy	2.000, 0.099	12	23 (23)	4	14	29	Dead
Kato 6	10	6/8	NA	F + M + 4Gy	1.706, 0.134	10	14 (55)	2	2	21	69
Kato 7	11	6/8	NA	F + M + 4Gy	1.149, 0.020	15.5	14 (39)	1	11	22	61
Kato 12	14	6/8	NA	F + M + 4Gy	1.628, 0.023	13	14 (18)	0	1	25 (2nd HCT)	26

HLA compatibility, genotypically human leukocyte antigen compatibility for graft-versus-host direction; VLCFA, very long chain fatty acid; CBT, cord blood transplantation; NFS, neurologic function scale; F + M + 4/3Gy, fludarabine, melphalan and total body irradiation of 4 or 3 Gy; Bs, Brain-sparing irradiation; NA, not available.
Fourteen cases of Kato 1, 2, 4, 6, 7, 8, 9, 10, 11, 12, 15, 16, Niizuma 1 and Awaya are collected from three references [3, 13, 14].

points [11]. Blood tests showed normal levels of adrenocorticotropin, cortisol, and electrolytes. VLCFA were accumulated in leukocytes to 1.800 (C24:0/C22:0, reference range 0.89–1.21), 0.064 (C25:0/C22:0, 0.018–0.030) and 0.077 (C26:0/C22:0, 0.007–0.019). Targeted sequencing determined a maternally inherited pathogenic mutation of NM_000033.4:c.1534 G > A (p.Gly512Ser) in *ABCD1*. The diagnosis of X-linked ALD was made within one month from his visit.

He was immediately referred to Kyushu University Hospital for HCT. On admission, he showed 120.3 cm (+0.9 SD) in height and 22.8 kg (+0.3 SD) in weight. Consciousness was alert and vital signs were stable. The ophthalmological test revealed a constriction in the lower-left field of the right eye. Intelligence quotient (IQ) was evaluated to be 85 on Japanese versions of Binet Intelligence Scale V. Autism screening by the Japanese version (ASQ-J) fulfilled the diagnostic criteria of ASD with the score of 17 (full score: 39, cut-off: 13). Symptoms scored 2 of the neurologic functional scale (full score: 25) [6]. The Loes score, 13 was on the upper limit of optimal condition (<12 points) for HCT.

For surrogate decision-making, parents continued discussions with core members specialized in pediatric hematology, oncology, endocrinology, neurology, neuroradiology and bioethics. Extensive, multidisciplinary discussions pointed out potential risks of neurological worsening associated with HCT (Table 1) [3,13,14]. The unfavorable outcomes included the progress of visual impairment, motor disability, cognitive deficits and endocrine dysfunctions after conditioning. The 10–20% rate of graft failure, GVHD and death was non-negligible [5]. Repeated discussion for 2 weeks reached a consensus for brain-sparing irradiated CBT.

Genotypically histocompatible cord blood was selected as an unrelated donor source. CB cells (nucleated cells 5.58×10^7/kg, $CD34^+$ cells 1.79×10^5/kg) were transfused after our standard regimen [12]. Because mild hyponatremia occurred during the chemotherapy, hydrocortisone (HDC) was administered as a replacement therapy (Fig. 1B). Neutrophil engraftment occurred at day 24. Donor chimerism was 82.8% at 1 month and 90.0% at 2 months posttransplant (Fig. 1B). Skin eruptions and diarrhea as grade II acute GVHD remitted after prednisolone therapy. In the follow-up test by the ophthalmologist, he was shown to develop a constriction in the lower-left field of the left eye on day 34. He was discharged from hospital at 65 days and achieved full donor chimerism at 5 months posttransplant. During 27 months, generalized seizures occurred three times but were controlled by lacosamide and clobazam. Presently, on full donor chimerism, he walks unaided without neurocognitive deterioration. Follow-up MRI showed stable demyelinating lesions without enlargement or progression (Fig. 1A). Mild cerebral atrophy was noticed in 4 weeks but not progressed for 2 years after CBT. In agreement with the time course, the effect of gadolinium enhancement disappeared at 4 weeks after CBT (Supplementary Fig. S1B).

4. Discussion

This report described a boy with ALD, who showed an advanced stage of brain lesions in MRI. Before making a critical decision, we considered it necessary to inform the parents that HCT may not necessarily warrant his survival to discharge or prevent the disease from further progression. Thus, we focused on repeating multidisciplinary discussions until we reached an unforced agreement on HCT with the parents. This process clarified that he could receive HCT with a tailored conditioning regimen to minimize the damage of brain tissues.

Allogenic HCT was established as an effective treatment modality for ALD. Successful outcomes of recipients have largely depended on the neurological state at the timing of HCT and on the sustained donor chimerism [6]. Earlier studies suggested that reduced intensity regimens lead to the low engraftment rate after HCT for childhood ALD [6]. However, modified protocols of HCT were recently shown to improve the engraftment rate to 94% (15 of 16 patients), 5-year survival to 91%, and achieved event-free survival of 60% for 5 years [3]. Thus, reduced intensity conditioning based on fludarabine, melphalan, and irradiation,

appeared to minimize the risk of fatal complications.

The degree of neurological deficits and the extent of cerebral demyelination are associated with the outcomes after HCT [6,7]. Besides the borderline stage with 13 Loes score in the patient, the demyelinating lesions extended to the bilateral internal capsules at diagnosis. Post-transplant neurological deterioration has been reported in similar cases with internal capsule involvement [3,5]. Specifically, all five children involving the internal capsules increased the Loes scores by 15 points or more in 2 to 7 months after HCT. In contrast, 10 of 11 patients involving no internal capsules showed the stable Loes score in 10–15 during median 18 months of observation period [3]. These data confirmed that the involvement of internal capsules was correlated with the outcome of CBT [3,13,14], where patients with the involvement of internal capsules showed more pronounced deteriorations in their Loes scores and NFS than those without the involvement (Table 1). Given this information, he was suspected to have more unfavorable course than the recovery to his base line of neurological functions pretransplant.

We thus rationalized that the immediate availability of HLA-matched donor, reduced-intensity conditioning with brain protection contributed to the engraftment of the donor graft and to preserving neurological functions, according to the previous report [13]. Compared to myeloablative regimen with busulfan and cyclophosphamide, reduced-intensity conditioning with fludarabine, melphalan, and brain-sparing irradiation minimizes the risk of fatal complications but not rejection. Both advantage and disadvantage of our regimen need to prospectively analyze in comparison with conventional methods.

It is important to reduce the time from the onset to the diagnosis and treatment of ALD. Ninety% of Japanese find a CB unit with 6/6 or 5/6 antigen-level HLA matches in JCBBN [15], which is an advantage for searching donors after the earliest diagnosis. Because an urgent decision-making is necessary in most cases of childhood-onset ALD, CBT with the brain-protecting protocol serves as a suitable strategy for affected children in Japan. However, it is important to note that disease progression continues for at least 6 months posttransplant and adrenal dysfunction is not corrected after HCT for cerebral disease. We thus emphasize the value of multidisciplinary discussions among immunohematologists, oncologists, child neurologists, neuroradiologists, endocrinologists and bioethicists for the borderline indication. This type of discussion continues for the borderline stage of cerebral ALD until the establishment of preclinical diagnosis, even in the era of newborn screening and gene therapy.

Funding

This study was supported by JSPS KAKENHI grant numbers JP19K08281 (Sakai), JP19K08867 (Koga); AMED under the grant number JP20ek0109411, 20wm0325002h; a research grant for prion diseases from the Ministry of Health, Labour and Welfare of Japan (JP20FC1054); The Japan Epilepsy Research Foundation, and Kawano Masanori Memorial Public Interest Incorporated Foundation for Promotion of Pediatrics (Sakai).

Author contributions

Yutaro Yada, Michiko Torio, Yuhki Koga, Fumiya Yamashita, Takuya Ichimura, Katsuhide Eguchi, Masataka Ishimura, Yuich Mushimoto, Ryutaro Kira and Yasunari Sakai managed the patient and analyzed the clinical data; Akio Hiwatashi analyzed and supervised the neuroimaging analysis; Momoko Sasazuki managed and supervised ethical discussion; Yutaro Yada, Michiko Torio, Yasunari Sakai and Shouichi Ohga drafted the manuscript; Shouichi Ohga conceptualized this study and revised the manuscript.

Declaration of Competing Interest

None.

Acknowledgments

We thank the patient and his parents for cooperating with our study; Nobuyuki Shimozawa (Professor, Gifu University) for enzymological and genetic diagnosis of ALD; Hiromasa Yabe (Professor, Tokai University) for helpful suggestion for conditioning; and Toshiro Hara (President, Fukuoka Children's Hospital) and our lab members for insightful comments.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2021.100778.

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