Case Report

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

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A R T I C L E  I N F O

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A B S T R A C T

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-old 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 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.

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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 (Chair 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/m² for 6 days), melphalan (70 mg/m² for 2 days), and brain-sparing total body irradiation at 4 Gy. Tacrolimus and 7–10 mg/m² 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 Loes score reached 13.

![Fig. 1. Clinical and neuroimaging features of the present case.](image)

(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, lamotrigine; CLB, clonazepam; GVHD, graft versus host disease; HCT, hematopoietic cell transplantation.
Table 1

| Case | Age at HCT (months) | Gender | HLA compatibility | Treatment | Conditioning regimen | VLCFA before HCT | VLCFA after HCT | NLS Before HCT | NLS After HCT | NLS Improvement | Study period (months) | NDI Before HCT | NDI After HCT | Diagnosis |
|------|---------------------|--------|-------------------|-----------|---------------------|------------------|----------------|----------------|----------------|-----------------|---------------------|----------------|----------------|-----------|
| Kato 1 | 8 | 4 | 8/8 | F | + | 20.0 × 10^9/day, 0.030 | 0.077 | 0.030 | 0.077 | 13 | 24 | (36) | 6 | 21 | 21 | 46 |
| Kato 2 | 15 | 5 | 6/8 | F | + | 1.710 × 10^9/day, 0.076 | 0.076 | 0.076 | 0.076 | 11 | 15.5 | (7) | 2 | 25 | 24 | 45 |
| Kato 3 | 12 | 6 | 6/8 | F | + | 1.950 × 10^9/day, 0.116 | 0.077 | 0.077 | 0.077 | 13 | 14 (27) | (7) | 2 | 16 | 8 | 14 |
| Kato 4 | 4 | 6 | 6/8 | F | + | 1.800 × 10^9/day, 0.077 | 0.077 | 0.077 | 0.077 | 13 | 10 | (27) | 2 | 3 | 24 | 6 |
| Kato 5 | 11 | 10 | 6/8 | F | + | 1.500 × 10^9/day, 0.056 | 0.056 | 0.056 | 0.056 | 16 | 14 | (58) | 1 | 3 | 20 | 76 |
| Kato 6 | 4 | 6 | 6/8 | F | + | 1.500 × 10^9/day, 0.056 | 0.056 | 0.056 | 0.056 | 16 | 14 | (58) | 1 | 3 | 20 | 76 |
| Kato 7 | 8 | 4 | 6/8 | F | + | 1.184 × 10^9/day, 0.020 | 0.020 | 0.020 | 0.020 | 14 | 12 | (52) | 1 | 3 | 19 | 76 |
| Kato 8 | 9 | 9 | 8/8 | F | + | 1.166 × 10^9/day, 0.018 | 0.018 | 0.018 | 0.018 | 18 | 14 | (72) | 2 | 8 | 24 | 45 |
| Kato 9 | 10 | 10 | 7/8 | F | + | 1.690 × 10^9/day, 0.089 | 0.089 | 0.089 | 0.089 | 14 | 22 (23) | (7) | 2 | 19 | 6 |
| Kato 10 | 6 | 10 | 6/8 | F | + | 1.706 × 10^9/day, 0.134 | 0.134 | 0.134 | 0.134 | 10 | 14 | (55) | 2 | 2 | 21 | 69 |
| Kato 11 | 12 | 14 | 6/8 | F | + | 1.429 × 0.026 | 0.026 | 0.026 | 0.026 | 13 | 10 | (23) | 2 | 1 | 22 | 6 |

VLCFA, very long chain fatty acid; CBT, cord blood transplantation; NFS, neurologic function scale; F, male; M, female; HCT, hematopoietic cell transplantation; VAD, vincristine, doxorubicin, and dexamethasone; HDG, high-dose glucocorticosteroids; NS, normal score; ASD, autism spectrum disorder; NDI, neurodevelopmental index; HDC, high dose cyclophosphamide; V, very; 10^3:10^4, 10^5, 10^6; SD, standard deviation.

Table 2

| Case | Age at HCT (months) | Gender | HLA compatibility | Treatment | Conditioning regimen | VLCFA before HCT | VLCFA after HCT | NLS Before HCT | NLS After HCT | NLS Improvement | Study period (months) | NDI Before HCT | NDI After HCT | Diagnosis |
|------|---------------------|--------|-------------------|-----------|---------------------|------------------|----------------|----------------|----------------|-----------------|---------------------|----------------|----------------|-----------|
| Kato 12 | 14 | 10 | 7/8 | F | + | 1.429 × 0.026 | 0.026 | 0.026 | 0.026 | 13 | 10 | (23) | 2 | 1 | 22 | 6 |

VLCFA, very long chain fatty acid; CBT, cord blood transplantation; NFS, neurologic function scale; F, male; M, female; HCT, hematopoietic cell transplantation; VAD, vincristine, doxorubicin, and dexamethasone; HDG, high-dose glucocorticosteroids; NS, normal score; ASD, autism spectrum disorder; NDI, neurodevelopmental index; HDC, high dose cyclophosphamide; V, very; 10^3:10^4, 10^5, 10^6; SD, standard deviation.

Table 3

| Case | Age at HCT (months) | Gender | HLA compatibility | Treatment | Conditioning regimen | VLCFA before HCT | VLCFA after HCT | NLS Before HCT | NLS After HCT | NLS Improvement | Study period (months) | NDI Before HCT | NDI After HCT | Diagnosis |
|------|---------------------|--------|-------------------|-----------|---------------------|------------------|----------------|----------------|----------------|-----------------|---------------------|----------------|----------------|-----------|
| Kato 13 | 14 | 10 | 7/8 | F | + | 1.429 × 0.026 | 0.026 | 0.026 | 0.026 | 13 | 10 | (23) | 2 | 1 | 22 | 6 |

VLCFA, very long chain fatty acid; CBT, cord blood transplantation; NFS, neurologic function scale; F, male; M, female; HCT, hematopoietic cell transplantation; VAD, vincristine, doxorubicin, and dexamethasone; HDG, high-dose glucocorticosteroids; NS, normal score; ASD, autism spectrum disorder; NDI, neurodevelopmental index; HDC, high dose cyclophosphamide; V, very; 10^3:10^4, 10^5, 10^6; SD, standard deviation.
transplant neurological deterioration has been reported in similar cases involving the internal capsules increased the Loes scores by 15 points or with internal capsule involvement [3,5]. Specifically, all five children lesions extended to the bilateral internal capsules at diagnosis. Post-showed more pronounced deteriorations in their Loes scores and NFS no internal capsules showed the stable Loes score in 10 borderline stage with 13 Loes score in the patient, the demyelinating functions, according to the previous report [13]. Compared to myeloloblastic regime 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.

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**Author contributions**

Yutaro Yada, Michiko Torio, Yuhi 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 Shouchi Ohga drafted the manuscript; Shouchi Ohga conceptualized this study and revised the manuscript.

**Declaration of Competing Interest**

None.

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**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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