Unrelated Umbilical Cord Blood Transplantation For Children With Hereditary Leukodystrophy: Single Center Experience

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Research

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Abstract

Background

Hereditary leukodystrophies are diverse metabolic diseases caused by gene mutations that result in the abnormal development or degeneration of myelin. Transplantation of matched sibling donor umbilical cord blood (UCB) can slow progression and prolong survival in some cases. For patients without siblings, however, UCB transplantation from unrelated donors may be the only option.

Methods

This retrospective study assessed unrelated UCB transplantation (UCBT) efficacy following busulfan- and cyclophosphamide-based myeloablative chemotherapy.

Results

The study cohort included 12 pediatric patients (ten males), nine with adrenoleukodystrophy (ALD) and three with globoid cell leukodystrophy (GLD), treated between April 2015 and March 2020. All received HLA-matched or partially mismatched UCBT. Median age at UCBT was 7.2 years (range, [0.8–12.9 years]). There were no cases of graft rejection. Median neutrophil engraftment time was 20 days [12–33 days] and median platelet engraftment time was 29 days [14–65 days]. Median follow-up was 28 months [1–73 months], and overall survival rate was 83.3% (10/12). Seven patients had higher *Loes* scores post-transplantation, and two patients died of infection. Four patients with rapid neurological deterioration pre-UCBT exhibited worse neurological symptoms post-UCBT. In contrast, four patients with stable neurological symptoms pre-UCBT demonstrated symptom stability post-UCBT, and two with no neurological symptoms pre-UCBT were also symptom-free post-UCBT. Further, lipid profiles of surviving ALD patients were improved post-treatment.

Conclusions

Hereditary leukodystrophy patients with mild neurological symptoms can benefit from UCBT, while UCBT cannot reverse advanced disease.

Introduction

Hereditary leukodystrophies are a rare group of inherited metabolic diseases caused by mutations in genes encoding metabolic enzymes or factors leading to abnormal development or diffuse damage to the myelin sheath. Adrenoleukodystrophy (ALD) is an X-linked β-oxidation disorder of very-long-chain fatty acids (VLCFAs) caused by *ABCD1* gene mutation [1]. More than 500 unique mutations in *ABCD1* associated with ALD have been identified [2]. The abnormal accumulation of metabolic substrates in the brain and adrenal cortex leads to progressive demyelination and adrenal cortex dysfunction [3]. Neurological symptoms include audiovisual deficits, mental retardation, cognitive impairments, behavioral abnormalities, and neuropsychiatric disorders. There are eight ALD subtypes, of which cerebral ALD in childhood accounts for about 30% of all cases and has the most severe clinical manifestations. After the onset of cerebral ALD, patients may exhibit disability and dementia followed by death in a few months to years [4]. Globoid cell leukodystrophy (GLD) is an autosomal recessive genetic disease caused by *GALC* mutations that cause demyelination through lack of galactocerebrosidase activity and ensuing accumulation of β-galactosides and derivatives. More than 270 different mutations in *GALC* related to GLD have been cataloged in the Human Gene Mutation Database [5]. Globoid cell leukodystrophy includes four clinical subtypes, early infantile phenotype, late infantile phenotype, juvenile phenotype, and adult phenotype. Patients with the early infantile phenotype are often younger than 6 months old and present with agitation, convulsion, audiovisual deficits, and feeding difficulties; further, the disease progresses rapidly, and median survival is only two years [6]. Alternatively, patients with the later-onset types present with dyskinesia, visual impairment, mental decline, and seizures [7].

In developed countries, newborn screening enables early diagnosis and intervention [8,9]. In developing countries like China, however, newborn screening does not include hereditary leukodystrophies. Further, early diagnosis is difficult due to the insidious onset, diversity, and non-specificity of symptoms. Dietary control and glucocorticoid administration may alleviate some symptoms, but these measures do not improve neurological deficits. Alternatively, allogeneic hematopoietic stem cell transplantation (allo-HSCT) can slow the progression of neuropathy and promote the long-term survival of children with cerebral ALD and GLD [8,10-12]. However, many

hereditary leukodystrophy patients lack a matched sibling donor (MSD) of hematopoietic stem cells. Therefore, it is critical that patients without an MSD find a suitable unrelated donor as soon as possible. Unrelated umbilical cord blood stem cells (UCB) which are advantageous due to easy isolation and low HLA compatibility requirements provide an alternative source of hematopoietic stem cells. As hereditary leukodystrophies are relatively rare, there are few case series on the efficacy of unrelated umbilical cord blood stem cell transplantation (UCBT). Here we report the outcomes of twelve consecutive patients receiving unrelated UCBT at a single center to identify the most promising candidates.

Patients And Methods

Patients

All hereditary leukodystrophy patients treated by unrelated UCBT from April 2015 to March 2020 at the Children's Hospital of Fudan University were included in this study. Diagnosis was based on clinical manifestations, enzyme detection, and neuroimaging examinations, and then confirmed by gene sequencing. All patients were younger than 18 years old and none had an MSD. All guardians provided written informed consent before transplantation and the study was approved by the ethics committee of the Children's Hospital of Fudan University (2016-162).

Chimeric Monitoring and Engraftment Definition

Donor-recipient chimerism was tested using the short tandem repeat technique at 2 weeks, 1 month, 2 months, 3 months, 6 months, 9 months, and 1 year after transplantation. More than 95% donor-derived cells was defined as complete donor chimerism. An absolute neutrophil count > 0.5×10^9/L for 3 consecutive days was defined as neutrophil engraftment, and platelet count > 20×10^9/L for 7 consecutive days without platelet transfusion was defined as platelet engraftment.

Neurological Function Scores, Performance Status, and *Loes* Scores

Each patient was assigned a Neurologic Function Score (NFS) pre- and post-UCBT based on evaluations of vision, hearing, communication, swallowing, urinary and fecal control, movement, and the presence of afebrile convulsions [13]. Performance status (PS) was scored by the Lansky standard [14]. In addition, a *Loes* score of cranial MRI lesion severity was assigned by a senior radiologist [15,16].

Supportive Treatment

All patients were cared for in an independent laminar flow ward before neutrophil engraftment. Ganciclovir (10 mg/kg/day, from the beginning of conditioning to day -1 pre-UCBT) and acyclovir (750 mg/m^2/day, from day 0 to day +270 post-UCBT) were used to prevent virus infection, caspofungin (from the beginning of conditioning to neutrophil engraftment) and voriconazole (from neutrophil engraftment to day +180) were used to prevent fungal infection, and sulfamethoxazole (25 mg/kg/day 2 days per week, from neutrophil engraftment to 6 months after immunosuppressant discontinuation) was used to prevent *Pneumocystis carinii* infection. Patients received intravenous immunoglobulin (500 mg/kg/dose) every 2 weeks starting on day +1 post-UCBT and continuing until B-lymphocyte count surpassed 200/μL.

Results

Clinical Conditions Before Transplantation

Twelve patients with hereditary leukodystrophy were treated by UCBT. Clinical and demographic characteristics of these patients (p1–p12) are summarized in Table 1. Nine (p1–p9 in Table 1) were diagnosed with cerebral ALD and harbored unique maternally inherited *ABCD1* mutations (mainly point mutations in exons 1 and 3), and the remaining three (p10–p12) were diagnosed with GLD and harbored inherited *GALC* gene mutations. The median onset age was 7 years (range, about 3 years to 11.9 years). Ten patients (all except p3 with ALD and p11 with GLD) had neurological symptoms before transplantation, eleven patients (all except p11) had abnormal brain white matter signals on cranial MRI before transplantation, and seven patients (p1, p3, and p5–p9) had adrenal cortex dysfunction and were receiving glucocorticoid replacement therapy. Serum VLCFAs were elevated in all ALD patients and leukocyte galactocerebrosidase activity was reduced in all GLD patients (see Table 1 for details).

Table 1. Baseline clinical characteristic of the 12 patients with heredity leukodystrophy

Patient	Sex	Onset age (years)	Gene defects	Mutations	Nervous system symptom	Lesions on cranial MRI	Adrenocortical insufficiency	VLCFAs	Galactocerebrosidase (nmol/17h/mg)
1	Male	8.3	ABCD1	exon1 c.829G > A, p. G277R	+	+	+	↑	NA
2	Male	7.0	ABCD1	exon1 c.593G > A, p. T198K	+	+	−	↑	NA
3	Male	about 3	ABCD1	exon3 c.1552C > T, p. R518W	−	+	+	↑	NA
4	Male	5.2	ABCD1	c.1992-2A > G, p?	+	+	−	↑	NA
5	Male	about 8	ABCD1	exon1 c.465delG p. E155Efs*43	+	+	+	↑	NA
6	Male	4.0	ABCD1	exon1 c.650A >c p. K217T	+	+	+	↑	NA
7	Male	6.3	ABCD1	exon 3–10 del	+	+	+	↑	NA
8	Male	7.2	ABCD1	exon 1 c.529C >T p. Q177X	+	+	+	↑	NA
9	Male	7.7	ABCD1	exon 10 c.2006A > G p.H669R	+	+	+	↑	NA
10	Female	7.5	GALC	exon 8 c.812G > A p. W271X exon 1 c.136G > T p. D46Y	+	+	NA	NA	4.76$ (12.89–100.93)
11	Female	–	GALC	exon 8 c.812G > A p. W271X exon 1 c.136G > T p. D46Y	−	−	NA	NA	6.47$ (12.89–100.93)
12	Male	4.3	GALC	exon 10 c.1090T > G p. L364V exon 1 c.136G > T p. D46Y	+	+	NA	NA	2.11$ (12.89–100.93)

NA, not applicable; MRI, magnetic resonance imaging; VLCFA, very-long-chain fatty acids

UCBT Data and Conditioning Regimen

Unrelated UCB was provided by the Chinese Cord Blood Bank with HLA matching at a minimum of 7/10 loci (Table 2) according to high-resolution typing identity of A, B, Cw, DRB1, and DQ. The median total nucleated cell (TNC) infused dose was 4.9×10^7/kg (range, 3.0×10^7 to 15.3×10^7/kg), and the median $CD34^+$ cell dose was 1.55×10^5/kg (range, 0.37×10^5 to 19.95×10^5/kg). The conditioning regimen included intravenous busulfan (BU, 12.8 mg/kg to 16 mg/kg), fludarabine (Flu, 150 mg/m^2), and cyclophosphamide (CY, 100

mg/kg). Rabbit anti-human thymocyte immunoglobulin (ATG, 5 mg/kg) was used in ten patients. Oral tacrolimus (FK506) was administered starting 4 days before transplantation to prevent graft versus host disease (GvHD). The target concentration of FK506 was 5–10 ng/mL. In addition to FK506, mycophenolate mofetil (MMF) was administered to the patient (p5) receiving UCB with 7/10 HLA matching on the first day post-transplantation. The median age at UCBT was 7.2 years (range, 0.8 to 12.9 years) and median body weight at UCBT was 24.3 kg (range, 8.5 to 38 kg). See Table 2 for details of each procedure.

Table 2. Basic characteristics of each umbilical cord blood stem cell transplantation procedure

Patient	UCBT age (years)	UCBT weight (kg)	HLA matching	TNC/kg $\times 10^7$	$CD34^+$/kg $\times 10^5$	Conditioning regimen	GvHD prophylaxis
1	8.8	38	8/10	5.2	1.25	BU/FLU/CY	FK506
2	7.8	25	10/10	3.4	0.37	BU/FLU/CY	FK506
3	6.2	24	8/10	4.4	0.57	ATG+BU/FLU/CY	FK506
4	5.5	17.5	8/10	7.2	1.34	ATG+BU/FLU/CY	FK506
5	12.9	36	7/10	3.8	1.22	ATG+BU/FLU/CY	FK506/MMF
6	5.0	20	8/10	6.4	3.20	ATG+BU/FLU/CY	FK506
7	6.5	23.5	8/10	5.2	0.82	ATG+BU/FLU/CY	FK506
8	8.2	24.5	8/10	4.6	3.29	ATG+BU/FLU/CY	FK506
9	8.2	38	9/10	3.0	1.76	ATG+BU/FLU/CY	FK506
10	8.0	22	10/10	5.3	7.32	ATG+BU/FLU/CY	FK506
11	0.8	8.5	9/10	15.3	19.95	ATG+BU/FLU/CY	FK506
12	4.5	24.5	8/10	3.7	3.22	ATG+BU/FLU/CY	FK506

UCBT, umbilical cord blood stem cell transplantation; HLA, human leukocyte antigen; ATG, antithymocyte globulin; Bu, Busulphan; Cy, Cyclophosphamide; Flu, Fludarabine; MMF, mycophenolate mofetil

Chimerism and Hematopoietic Reconstitution Post-UCBT

All patients demonstrated complete donor chimerism (CDC) by day +14, and the chimerism was stable during follow-up. The median neutrophil engraftment time was 20 days (range, 12 to 33 days) and the median platelet engraftment time was 29 days (range, 14 to 65 days) after transplantation.

Prognosis and Transplant-related Complications

The median follow-up time after UCBT was 28 months (range, 1 to 73 months). Of the 12 patients treated, two died (both with ADL), one of severe pneumonia complicated by sepsis within one month after UCBT and the other of severe pneumonia due to rapid progression of neurological symptoms five months after UCBT, for an overall survival rate of 81.8%. Four patients (33.3%) developed grade II acute GvHD, and all responded to methylprednisolone therapy. There were no cases of chronic GvHD. Half of the patients developed pulmonary infection after transplantation, including the two fatalities. Four cases developed cytomegalovirus (CMV) viremia, all of which responded to ganciclovir and/or foscarnet as confirmed by negative CMV-DNA tests. Two patients (16.7%) developed delayed hemorrhagic cystitis caused by BK virus infection, and both cases gradually eased after hydration, dieresis, and indwelling catheterization. Two patients (16.7%) developed urinary tract infections after transplantation that were successfully treated with sensitive antibiotics. Finally, one male patient developed autoimmune hemolytic anemia after transplantation that was controlled by plasma exchange, rituximab, and methylprednisolone. However, neurological symptoms deteriorated rapidly. See Table 3 for details of post-UBCT complications and treatments.

Table 3. Outcomes and complications of UCBT

Patient	Engraftment	Chimerism	Neutrophil engraftment day	Platelet engraftment day	GvHD	Complication	Outcome (months post-UCBT)
1	Engrafted	CDC	19	22	I	Pulmonary fungal infection	Alive (73)
2	Engrafted	CDC	32	-	-	Severe pneumonia, septic shock Gastrointestinal hemorrhage	Died (1)
3	Engrafted	CDC	33	37	I	None	Alive/well[#] (41)
4	Engrafted	CDC	21	26	II	Urinary tract infection Pneumonia, CMV viremia	Alive (38)
5	Engrafted	CDC	22	43	II	Severe pneumonia (*Klebsiella pneumoniae, Candida tropical*) Septic shock CMV viremia	Died (5)
6	Engrafted	CDC	12	14	I	Severe pneumonia (*Acinetobacter baumannii*) CMV viremia AIHA	Alive (30)
7	Engrafted	CDC	18	29	II	Hemorrhagic cystitis	Alive (26)
8	Engrafted	CDC	24	35	I	None	Alive (21)
9	Engrafted	CDC	19	29	II	Hemorrhagic cystitis, Pneumonia	Alive (18)
10	Engrafted	CDC	16	17	I	Urinary tract infection	Alive (46)
11	Engrafted	CDC	25	37	I	None	Alive/well[#] (37)
12	Engrafted	CDC	14	65	I	CMV viremia	Alive (20)

AIHA, autoimmune hemolytic anemia; CDC, complete donor chimerism; [#] Nervous system asymptomatic

Comparison of Neurologic Function Score, Performance Status, and Loes Score Pre-UCBT and Post-UCBT

Neurologic function, PS, and *Loes* scores were evaluated before and regularly after transplantation. Eight patients with ALD (all except p3) and two patients with GLD (all except p11) demonstrated neurological impairments of varying severity before transplantation (NFS range, 1–17 points), and two of these patients (both with ALD) died after UCBT. Eleven patients (all except p2) were followed-up for at least three months after transplantation, and all showed varying degrees of neurologic symptom aggravation. In patient 6, neurologic symptoms deteriorated markedly after transplantation (6 points before transplantation to 9 points three months after transplantation to 24 points six months after transplantation) due to severe autoimmune hemolytic anemia, and there was no significant recovery during follow-up. Among the remaining seven patients (p1, p3, p4, p6–p9), the NFS of p1 was similar to pre-UBCT baseline at 5 years follow-up (Figure 1 for details). All other ALD cases demonstrated different degrees of brain damage before transplantation as measured by *Loes* scoring of magnetic resonance images, and most exhibited further increases in brain lesion severity after UCBT with stabilization by nine months post-treatment.

Two female patients (p10 and p11) with GLD were siblings. The neurological symptoms of the elder sibling (p10) progressed slowly before and after transplantation as evidenced by stable NFS and PS. Similarly, the younger sibling (p11) had no imaging lesions or nervous system involvement before or after UCBT. Another male (p12) with GLD was also neurologically stable before and after UCBT, although the *Loes* score increased slightly after transplantation. The changes in *Loes* scores for each patient throughout the treatment

period are shown in Figure 2. Finally, the PS of six patients (p3, p7, p8, p10, p11, and p12) was stable after UCBT, while all other patients demonstrated different degrees of PS deterioration (Table 4).

Table 4. Performance status scores of patients with heredity leukodystrophy pre-UCBT and post-UCBT

Patient	PS pre-UCBT	PS post-UCBT[&]
1	70	50
2	80	0
3	100	100
4	50	40
5	60	0
6	50	40
7	100	100
8	80	80
9	50	40
10	80	80
11	100	100
12	80	80

performance status scores (PS) by Lansky [14]; [&]at last follow-up

Changes in Lipid Metabolism

The serum VLCFA concentrations of most surviving ALD patients (except p4) were measured regularly following treatment. Both absolute C26:0 concentration and the C26:0/C22:0 ratio were significantly reduced one year post-UCBT (Figure 3), indicating partial restoration of ABCD1 activity.

Discussion

Treatment of hereditary leukodystrophy is limited by a lack of effective drugs. Diet adjustment and glucocorticoids may alleviate some symptoms, but cannot improve neuropathy, which is the predominant cause of functional impairment and frequently an indirect cause of death from infection. Currently, hematopoietic stem cell transplantation is the only way to prevent the progression of neuropathy and prolong survival. Cerebral type ALD and GLD in childhood are both indications for HSCT [11], while ADL patients with genetic diagnosis but mild or absent symptoms should instead receive regular MRI and neurological examinations to assess myelination status. Once cerebral manifestations occur, transplantation should be conducted as early as possible to prevent further progression and improve prognosis [17].

The benefits of HSCT for GLD are attributed to "cross correction", a process in which the GALC enzyme secreted by donor cells binds to surface receptors on recipient host cells and is accumulated by pinocytosis, thereby compensating for the enzymatic deficit. If GALC activity is sufficient, demyelination and neuropathy may be prevented [18]. In contrast, the therapeutic mechanisms of HSCT for ALD are still unclear. It has been proposed that monocytes from the donor can cross the blood–brain barrier and differentiate into microglia, and that these microglia help restore ABCD1 activity [19].

The neuropathy associated of childhood cerebral ALD and GLD progresses rapidly, so timely transplantation is critical. The European Society for Blood and Marrow Transplantation recommends related donors as the first choice for stem cell transplantation, followed by unrelated donors with at least 4/6 site matching. UCB is easy to obtain and rich in stem cells [18]. However, the failure rate of UCB engraftment is higher than that of bone marrow or peripheral blood stem cells, so myeloablative conditioning should be used prior to transplantation. In this study, twelve patients were treated with BU/CY- based myeloablative conditioning and all demonstrated complete donor cell chimerism two weeks after transplantation that remained stable during follow-up.

Ten patients with hereditary leukodystrophy had nervous system symptoms before transplantation. However, the median time from onset to UCBT was 6 months (2 to 58 months), which may explain the continued deterioration in some patients after treatment. At present, hereditary leukodystrophies are not part of neonatal screening in China. In most patients, the initial symptoms are non-specific, so diagnosis is often delayed, resulting in progression of neuropathy before transplantation. In our group of ALD patients, both *Loes* and NFS scores indicated substantial structural and functional neurological impairment before transplantation. Although neurological function was generally more stable following transplantation, pretreatment damage was largely irreversibly, underscoring the urgency of diagnostic confirmation and treatment.

In previous reports, the overall survival rates of cerebral ALD and GLD following UCBT ranged from 59–69% and 43–100%, respectively, and analysis of prognostic factors showed that early-stage disease (no neurological symptoms or mild symptoms), fewer and less extensive brain imaging lesions, and sufficient stem cells were all predictive of better prognosis [11,13,20,21]. For GLD patients, transplantation reduced the risk of death by 45% [22]. Asymptomatic GLD newborns can obtain 100% engraftment and 100% survival through UCBT. After transplantation, the myelin gradually forms and skills development gradually improves [21].

GvHD and infection are common complications following transplantation. Compared to stem cells from bone marrow or peripheral blood, the immunogenicity of UCB is lower, so the incidence of severe GvHD after UCBT is relatively reduced (only about 20–35% in previous reports) [11]. In the current study, there were no cases of chronic or severe GvHD, only four cases of acute grade II GvHD responsive to glucocorticoid therapy. Children with hereditary leukodystrophy may have weak cough reflexes and urinary incontinence due to neuropathy as well as poor immune function after pretreatment, which in combination can increase the risks of pulmonary and urinary tract infections. Indeed, previous studies have found that severe infection associated with disease progression after transplantation is the main cause of death among children with hereditary leukodystrophy [11]. In the present study, six of twelve patients developed pulmonary infection after transplantation, and two died, while another four developed CMV viremia. Fortunately, these CMV viremia cases were cured by ganciclovir or foscarnet treatment. In addition, the two case of urinary tract infection and the two cases of hemorrhagic cystitis were improved by antibiotic treatment or support therapy. Therefore, clinical outcome following UCBT for hereditary leukodystrophy may be improved by more intensive nursing care to prevent pulmonary infection.

Multiple factors can affect the prognosis of neurological function in hereditary leukodystrophy patients after transplantation, including disease severity before transplantation, donor chimerism level after transplantation, GvHD severity, and other transplantation related complications, especially pulmonary infection. At present, most studies on prognosis have focused on survival rate, while few studies have conducted longitudinal assessment of nerve function [23]. Peters and colleagues found that only 16% of patients with neurological deficits before transplantation demonstrated improvement after transplantation, while 56% of patients without neurological deficits before transplantation had no neurological deficits following transplantation [24]. Van den Broek and colleagues found that 50% of hereditary leukodystrophy patients with a mild decline in functional status score before transplantation remained stable after transplantation, while 50% exhibited neurological deterioration after transplantation [11]. In such cases, disease progression may occur due to enzyme insufficiency before substantial engraftment.

We also found that lesion severity does not necessarily predict post-treatment outcome. Rather, neurological function may be the predominant predictive factor. Patient 7 had a relatively high *Loes* score before transplantation, while neurological function score was relatively low (NFS = 1) with no audiovisual dysfunction, and this patient obtained the greatest benefit after transplantation (NFS = 1). Thus, audiovisual function before transplantation may be a good predictor of prognosis.

Conclusions

Unrelated UCB transplantation is more effective for hereditary leukodystrophy patients with mild or no neurological symptoms, so early diagnosis and timely treatment prior to substantial progression are critical. For these patients lacking MSD, unrelated UCBT is safe and effective. In contrast, the potential value of UCBT for children with rapid disease progression and severe neurological impairment may be limited, so parental expectations should be carefully managed.

Declarations

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Authorship Contributions

(I) Conception and design: Ping Wang，Xiaonan Du, Quanli Shen, Xiaowen Qian，Xiaowen Zhai; (II) Administrative support: Hongsheng Wang, Shuizhen Zhou, Yi Wang, Xiaowen Zhai; (III) Provision of study materials or patients: Wenjin Jiang, Shuizhen Zhou, Yi Wang, Xiaowen Qian; (IV) Collection and assembly of data:Ping Wang，Xiaonan Du, Quanli Shen,Chen Shen; (V) Data analysis and interpretation: Ping Wang，Xiaonan Du, Quanli Shen,Wenjin Jiang, Chen Shen,Hongsheng Wang ; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All guardians provided written informed consent before transplantation and the study was approved by the ethics committee of the Children's Hospital of Fudan University (2016-162).

Consent for publication

Participants were informed that the results may be published in a peer-reviewed medical journal (no individual data).

Competing interests

The authors declare that they have no competing interests.

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Figures

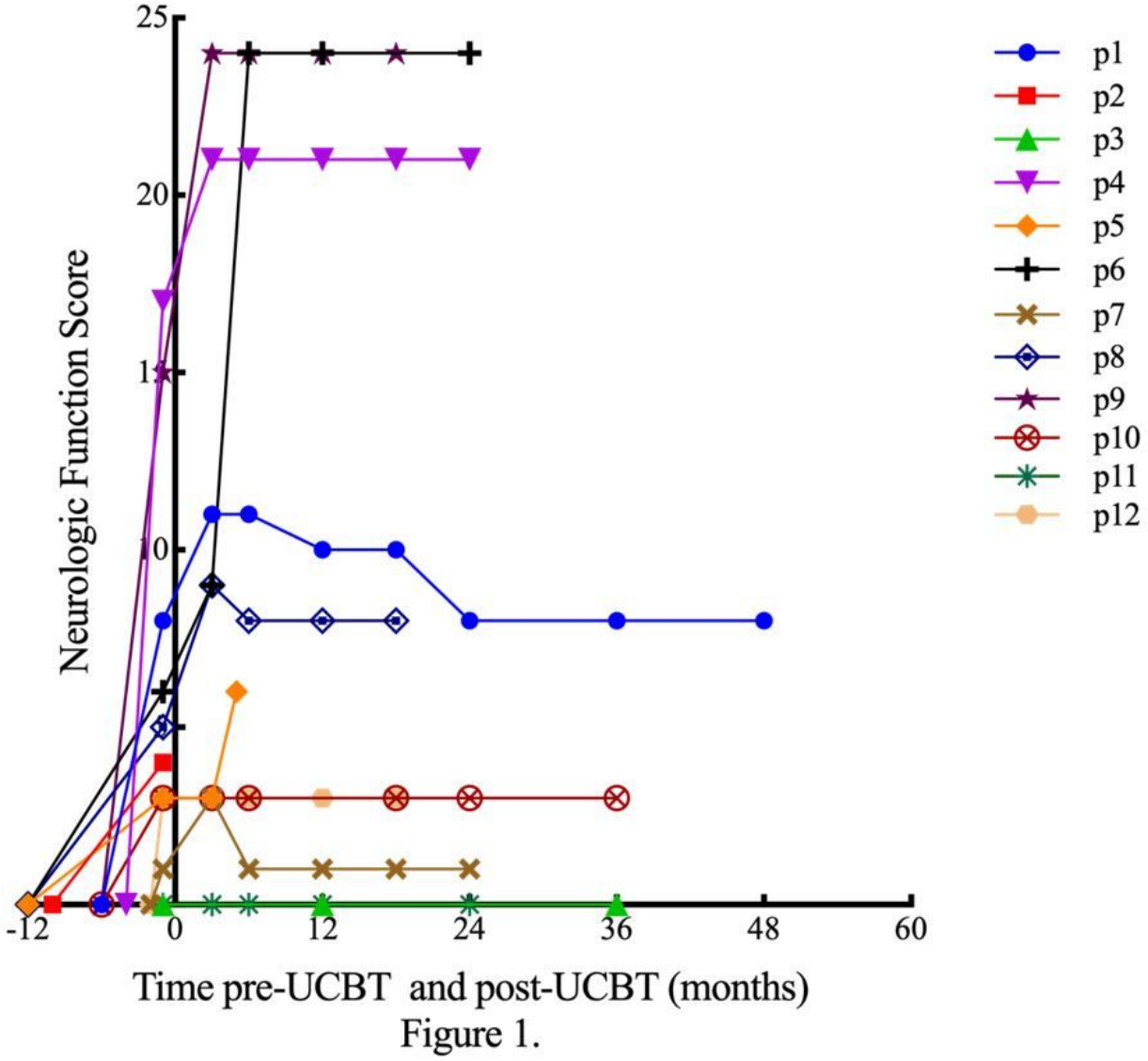

Figure 1.

Figure 1

Time course of Neurologic Function Score changes for all patients.

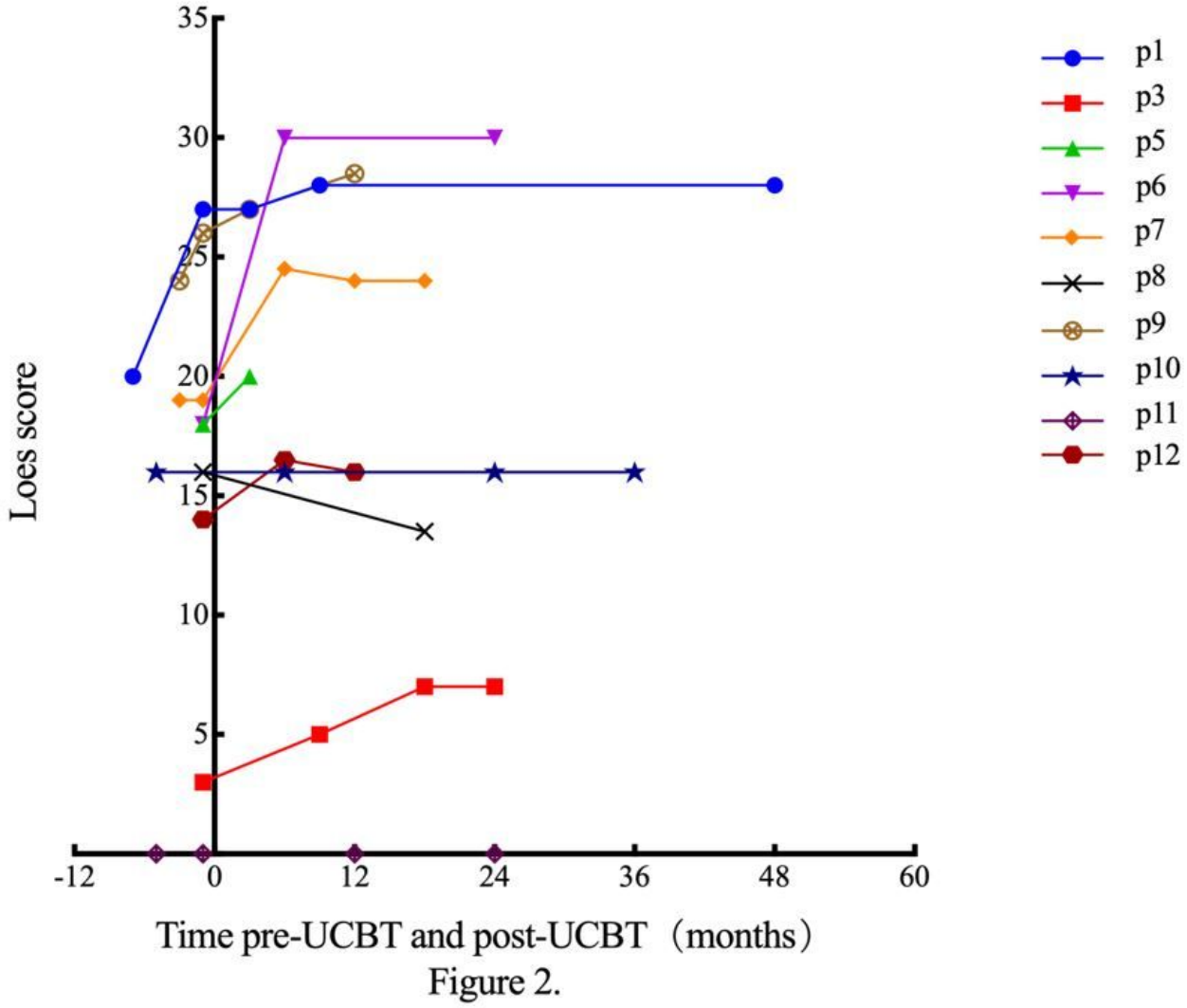

Figure 2

Time course of Loes score changes for all patients. In some cases, there was no post-UCBT data because of early death (p2) or because the parent (of p4) refused MRI examination after transplantation.

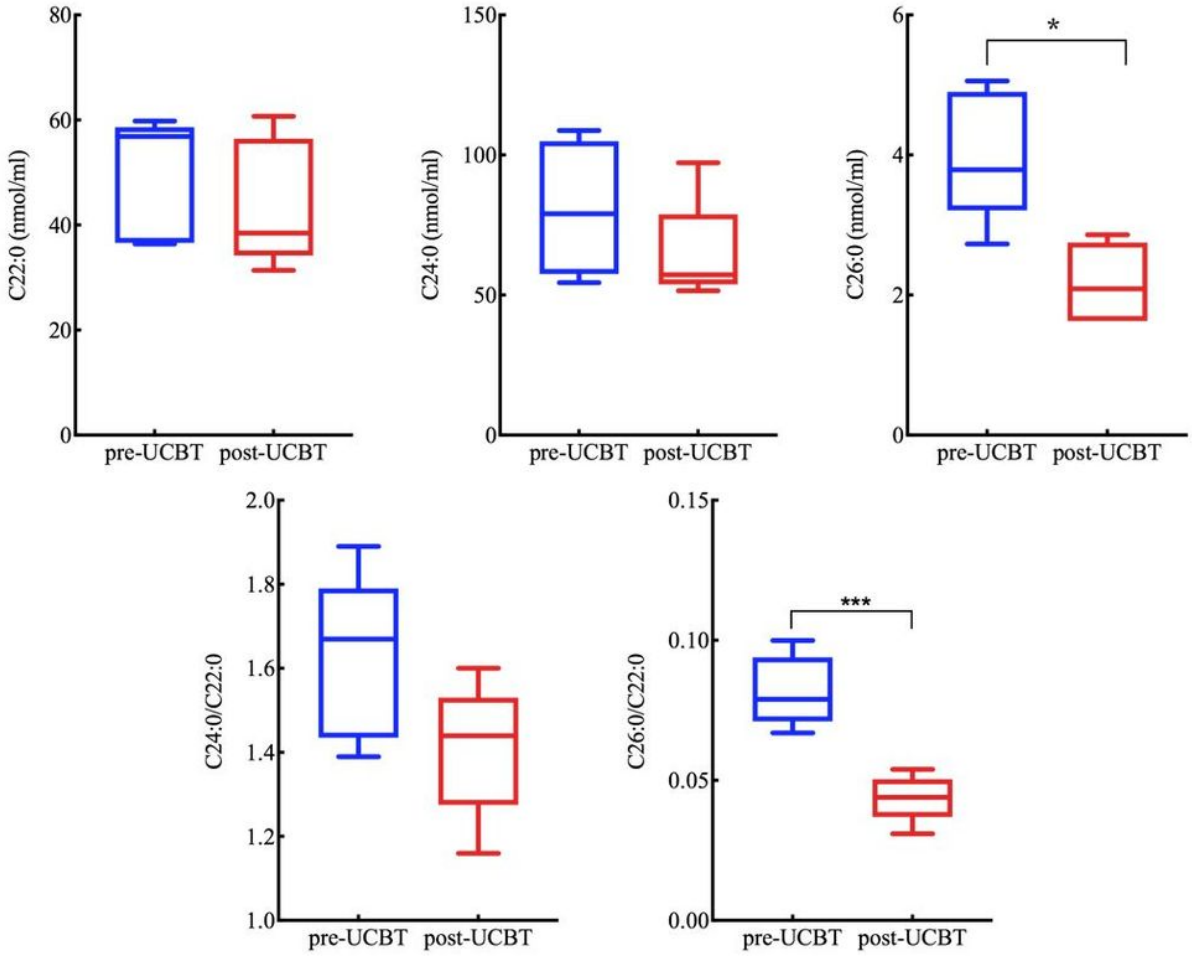

Figure 3

Serum very-long-chain fatty acid (VLCFA) concentrations for all ALD patients (excluding p2, p4, and p5 without post-UCBT data) were reduced one year post-UCBT. (reference value C22:0 ≤ 96.3 nmol/mL, C24:0 ≤ 91.4 nmol/mL, C26:0 ≤ 1.30 nmol/mL, C24:0/C22:0 ≤ 1.39, C26:0/C22:0 ≤ 0.023) * means $P < 0.05$ *** means $P < 0.001$