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CASE REPORT

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Living-donor liver transplantation for mild Zellweger spectrum disorder: Up to 17 years follow-up

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Abstract

Mild Zellweger spectrum disorder, also described as Infantile Refsum disease, is attributable to mutations in PEX genes. Its clinical course is characterized by progressive hearing and vision loss, and neurodevelopmental regression. Supportive management is currently considered the standard of care, as no treatment has shown clinical benefits. LT was shown to correct levels of circulating toxic metabolites, partly responsible for chronic neurological impairment. Of three patients having undergone LT for mild ZSD, one died after LT, while the other two displayed significant neurodevelopmental improvement on both the long-term (17 years post-LT) and short-term (9 months post-LT) follow-up. We documented a sustained improvement of biochemical functions, with a complete normalization of plasma phytanic, pristanic, and pipecolic acid levels. This was associated with stabilization of hearing and visual functions, and improved neurodevelopmental status, which has enabled the older patient to lead a relatively autonomous lifestyle on the long term. The psychomotor acquisitions have been markedly improved as compared to their affected siblings, who did not undergo LT and exhibited a poor neurological outcome with severe disabilities. We speculate that LT performed before the onset of severe sensorineural defects in mild ZSD enables partial metabolic remission and improved long-term clinical outcomes.

KEYWORDS

inborn error of metabolism, Infantile Refsum disease, living-donor liver transplantation, neurodevelopmental outcome, peroxisome biogenesis disorder, Zellweger spectrum disorder

1 | INTRODUCTION

ZSD is a clinical spectrum of diseases due to abnormal formation and function of peroxisomes, attributable to defective peroxins that are encoded by the PEX genes.[1] The manifestations of these inborn errors of metabolism are seen as a continuum between the severe Zellweger syndrome (OMIM #214100) and the milder Heimler syndrome (OMIM #234580, #616617). Clinical presentation varies from death in infancy to neurodevelopmental delays among those who survive beyond the first decade of life.[2,3] Among the long-term survivors, the lack of independent living skills is the most noticeable and handicapping. Characteristically elevated levels of phytanic, pristanic, pipecolic, and VLCFA, and bile acid intermediates are observed in the plasma of affected children. Additionally, the plasmalogen concentration in RBC membranes is decreased. The current standard of care consists of avoiding exposure to phytanic acid,[4] which is suggested to exert a direct toxic effect on neurological tissues.[5] We previously demonstrated the short-term benefit of LT[6] and LCT[7] on biochemical and clinical outcome, as reported for other organelle disease.[8,9] We have herein reported our broadened experience, describing the long-term

Abbreviations: BERA, brainstem-evoked response audiometry; DQ, developmental quotient; LCT, liver cell transplantation; LT, liver transplantation; RBC, red blood cell; VLCFA, very-long-chain fatty acids; ZSD, Zellweger spectrum disorder.

outcome of the same individual who received an LT 17 years ago, while including other LT recipients for the same indication.

2 | PATIENT DESCRIPTION

The demographic description, clinical features at initial presentation, diagnostic characteristics, and LT details are given in Table 1. Patient 1 (P #1) was diagnosed with mild ZSD at an early age before severe neurological handicap developed. Her older affected sibling was already severely handicapped and exhibited advanced sensorineural impairment. P #1 underwent an LT after approval by the institutional ethics committee and following receipt of informed consent from the family concerning the theoretical basis of the treatment. Following LT, significant improvement was seen in the quality of life and other aspects, as previously reported by our team at 2 years post-LT.[6] P #3's parents approached us to perform an LT for their child, as available treatments did not prove clinically beneficial. When he underwent LT, their 2-year-old son was unable to stay in a sitting position, and his older affected sibling was severely handicapped.

A third patient (P #2) received an LT for the same indication, but died suddenly 18 days afterward due to an acute hypotension episode with hyperkalemia (8.51 mmol/L) and hyponatremia (127.5 mmol/L). The follow-up in this patient was too short for the assessment of any clinical or neurodevelopmental improvement and has therefore not been described below; the patient characteristics and biochemical evolution are, however, mentioned in Tables 1 and 2. In the following study, we have shared our long-term data pertaining to biochemical, clinical, and neurodevelopmental responses in P #1 and P #3.

3 | BIOCHEMICAL RESPONSE IN MILD ZSD AFTER LIVER TRANSPLANTATION

A significant and sustained improvement in both children's biochemical profile was noticed. These children exhibited increased VLCFA, phytanic, pristanic, and pipecolic acid levels, and decreased RBC membrane plasmalogen concentration at diagnosis (Table 1). Pre-LT C26:C22 ratios in P #1 and P #3 were 27xULN and 7xULN, respectively, showing a dramatic decrease soon after LT. Both children maintained C26:C22 ratios under 4xULN at last biochemical follow-up (ie, at 17 years and 9 months post-LT, respectively). Plasma pipecolic levels normalized in P #1 until 15 years post-LT, after which a gradual increase was observed, whereas P #3 displayed normal levels until last follow-up (Figure 1, Table 2). Plasma phytanic and pristanic acid levels after LT remained normal in both children. Post-LT C_{27}-bile acid intermediates (dihydroxycholestanoic acid and trihydroxycholestanoic acid) were undetectable in P #1, and plasmalogen content in RBC showed fluctuating levels in all children.

4 | SENSORINEURAL RESPONSE IN MILD ZSD AFTER LIVER TRANSPLANTATION

For both children, sensorineural responses, including vision and hearing, improved in certain aspects, while there was no further worsening, that is, stabilization of function, for others (Figure 2, Table S2). As these are slowly evolving changes, they could be better observed in P #1 with a significantly longer follow-up duration.

P #1's auditory acuity assessed by BERA remained nearly stable post-LT (60 dB pre-LT and 80 dB at 7 years post-LT). At the age of 13 years, *that is*, 12 years post-LT, she successfully underwent a cochlear implant insertion in the left ear because of chronic suppurative otitis media. For P #3, serial BERA has not been performed yet, and he continues to utilize the same hearing aids as before.

Significant improvement in nystagmus was observed post-LT in P #1. Vision deterioration arrest was noticed in P #1, in which visually evoked potentials remained normal, without any cataract formation. The electroretinogram pre-LT displayed reduced scotopic amplitude (70 and 50 μV for left and right eyes, respectively), combined with a tigroid retinitis pigmentosa in the eye fundus. Her visual acuity is 1/10 and showed no evolution after after LT.

5 | GROWTH AND DEVELOPMENT RESPONSE IN MILD ZSD AFTER LIVER TRANSPLANTATION

The long-term follow-up of P #1 indicated that she consistently developed according to her growth curve concerning height (−3.7 standard deviation [SD] at last follow-up), weight (−4.3 SD at last follow-up), and head circumference (−2 SD at last follow-up) from the age of 6 months, *that is*, since her LT. Her pubertal growth spurt was remarkably well sustained, and she attained menarche at the age of 15 years. For P #3, a similar analysis would need a longer follow-up duration, which is not available.

To assess developmental progress, we calculated developmental quotient (DQ = normal age of milestone acquisition divided by chronological age) across motor and language spheres sequentially after LT. DQ was based on the Denver Developmental Screening Test when available[10] and otherwise on the Milestone Checklists[11] (Figure 3, Table S3).

After transplantation, P #1 acquired several milestones, though with delay. She is currently autonomous after having acquired independent living skills, is being educated in a school for the visually impaired, and has social interactions. There is a strong contrast in comparison with her elder sister with the same disease, as she is totally dependent on care for her daily activities. P #3 experienced a dramatic improvement in his social interaction skills in his 9 months of post-LT life, as he has become more responsive to verbal and non-verbal communication. He has additionally acquired the sitting position without the support and is able to stand with support at 9 months post-LT, which he had never been able to do before.

6 | ALLOGRAFT FUNCTION

Allograft outcome in terms of liver function (Table S1), rejection episodes, fibrosis evolution, immune-suppression requirement,

TABLE 1 Demographic description, clinical features at initial presentation, diagnostic characteristics, and LT details of the patients

Characteristics	Patient 1	Patient 2	Patient 3
Demographics			
Age at initial presentation	1 mo	2 mo	2 mo
Gender	Female	Female	Male
Ethnicity	Caucasian	Caucasian	Syrian-Chinese
Clinical features			
Family history	Elder sibling diagnosed with a mild ZSD	First child of the couple	Elder sibling diagnosed with a mild ZSD
Antenatal and natal history	Small for gestational age (birth weight <P3)	Chronic fetal distress, dilated colon	Nothing significant
At presentation	Facial dysmorphism, feeding disturbances, nystagmus, axial hypotonia and hepatomegaly	Facial dysmorphism, steatorrhea	Facial dysmorphism, nystagmus, axial hypotonia, peripheral hypertonia, hepatomegaly
Brain MRI	Normal, no leukodystrophy	Normal, no leukodystrophy	Polymicrogyria
Diagnostic characteristics			
Plasma VLCFA			
C 26:0 (0.45-1.32 μmol/L)	8.93 (6.8× ULN)	6.11 (4.6× ULN)	2.26 (1.7× ULN)
C 24: C 22 (0.32-1.11)	2.08 (1.9× ULN)	1.48 (1.3× ULN)	1.36 (1.2× ULN)
C 26: C 22 (0-0.02)	0.55 (27.5× ULN)	0.25 (12.5× ULN)	0.15 (7.5× ULN)
Plasma phytanic acid (0-9 μmol/L)	0.3 (within normal range)	18.58 (2.1× ULN)	30.47 (3.4× ULN)
Plasma pristanic acid (0-3 μmol/L)	Not done	6.38 (2.1× ULN)	7.22 (2.4× ULN)
Plasma pipecolic acid (0.6-4.1 μmol/L)	34 (8.3× ULN)	Not done	450 (109.8× ULN)
RBC membrane plasmalogens			
C16 DMA: C16 FA (0.046-0.082)	0.044 (0.96× LLN)	0.122 (1.49× ULN)	0.047 (within normal range)
C18 DMA: C18 FA (0.115-0.265)	0.105 (0.91× LLN)	0.165 (within normal range)	0.019 (0.17× LLN)
Genetic evaluation	PEX1 heterozygote c.3710A>C; unknown p.Ala1237Glu; unkown	PEX12 compound heterozygote c.126+1G>T; c.1047_1049delACA splicing defect; p.Gln349del	PEX1 compound heterozygote c.547G>A; c.1099del p.Arg183Ter; p.Gln367LysfsTer20
Pre-LT treatment	Low-phytanic acid diet and DHA	Vitamin D & K and calcium	DHA
LT details			
Donor	Living-related	Living-related	Living-related
Age of donor	30 y	45 y	34 y
Age of recipient at LT	7 mo	24 mo	25 mo
IS post-LT			
Induction	Tacrolimus + corticosteroids	Tacrolimus + basiliximab	Tacrolimus + basiliximab
Maintenance	Tacrolimus + mycophenolate mofetil	Tacrolimus monotherapy	Tacrolimus monotherapy
Number of ACR	2	1	0
Complications	CMV colitis, cholangitis, biliary stenosis, *C. difficile* infection, intrahepatic abscess	Deceased of unrelated causes 18 d post-LT	CMV infection, *C. difficile* infection

The values are shown as number of times of the upper/lower limit of the normal between parentheses.
LT, liver transplantation; ZSD, Zellweger spectrum disorder; MRI, magnetic resonance imaging; VLCFA, very-long-chain fatty acids; ULN, upper limit of the normal; LLN, lower limit of the normal; RBC, red blood cell; DMA, dimethylacetals; FA, fatty acids; DHA, docosahexaenoic acid; IS, immunosuppression; ACR, acute and chronic rejections; CMV, cytomegalovirus.

TABLE 2 Biochemical parameters pre-LT and post-LT

	Plasma VLCFA						RBC membrane plasmalogens	
Time of measure	C 26:0 (0.45-1.32 μmol/L)	C 24: C 22 (0.32-1.11)	C 26: C 22 (0-0.02)	Plasma phytanic acid (0-9 μmol/L)	Plasma pristanic acid (0-3 μmol/L)	Plasma pipecolic acid (0.6-4.1 μmol/L)	C16 DMA: C16 FA (0.046-0.082)	C18 DMA: C18 FA (0.115-0.265)
Patient 1								
5 mo pre-LT	8.93	2.076	0.547	0.3[a]		34	0.044	0.105
3 mo pre-LT	7.06	1.56	0.303	1.6[a]				
1 d post-LT	1.9	1.162	0.152	1.34		2.19		
1 mo post-LT	2.87	1.139	0.178	1.2	5.39			
2 mo post-LT	1.84	1.246	0.046	0.43				
3 mo post-LT	1.16	1.322	0.074	0		2.06	0.064	0.134
4 mo post-LT	2.23	1.375	0.062	0			0.038	0.101
5 mo post-LT	2.6	1.389	0.081	0			0.046	0.108
6 mo post-LT	2.22	1.197	0.058	0	0	1	0.045	0.11
9 mo post-LT	1.96	1.266	0.063	0.81				
11 mo post-LT	3.06	1.373	0.102	1.3				
12 mo post-LT	3.02	1.191	0.073	6.4				
13 mo post-LT	3.4	1.187	0.1	6.4			0.06	0.14
2 y post-LT	0.49	1.393	0.094	0.35	0.77	1	0.035	0.121
3 y post-LT	0.51	0.842	0.012	2.11	0.07	1.8		
15 y post-LT	5.64	1.212	0.112	1.32	0.23	1.7		
16 y post-LT	4.96	1.226	0.077	3.26	0.1	6.5	0.058	0.055
17 post-LT	5.14	1.056	0.074	1.92	0.27	11.7		
Patient 2								
13 mo pre-LT	5.76	1.428	0.245	15.77	6.37			
11 mo pre-LT	6.11	1.478	0.246	18.58	6.38		0.122	0.165
12 d post-LT	2.32	1.097	0.058	0.95	0.14			
Patient 3								
2 mo pre-LT	2.26	1.043	0.081	30.47	7.22	254		
1 mo pre-LT	1.75	1.362	0.151	16.54	3.9	450	0.047	0.019
2 d post-LT	1.05	1.064	0.045	5.33	0.83			
1 mo post-LT	2.51	1.085	0.069	3.91	0.4	2.5		
4 mo post-LT	2.28	1.407	0.08	6.87	0.86	2.3	0.052	0.055
9 mo post-LT	1.86	1.249	0.059	3.14	0.21	2.3		

[a]Normal value attributable to young age (inadequate duration for the accumulation of phytanic acid). The normal values are shown in parentheses.
LT, liver transplantation; VLCFA, very-long-chain fatty acids; RBC, red blood cells; DMA, dimethylacetals; FA, fatty acids.

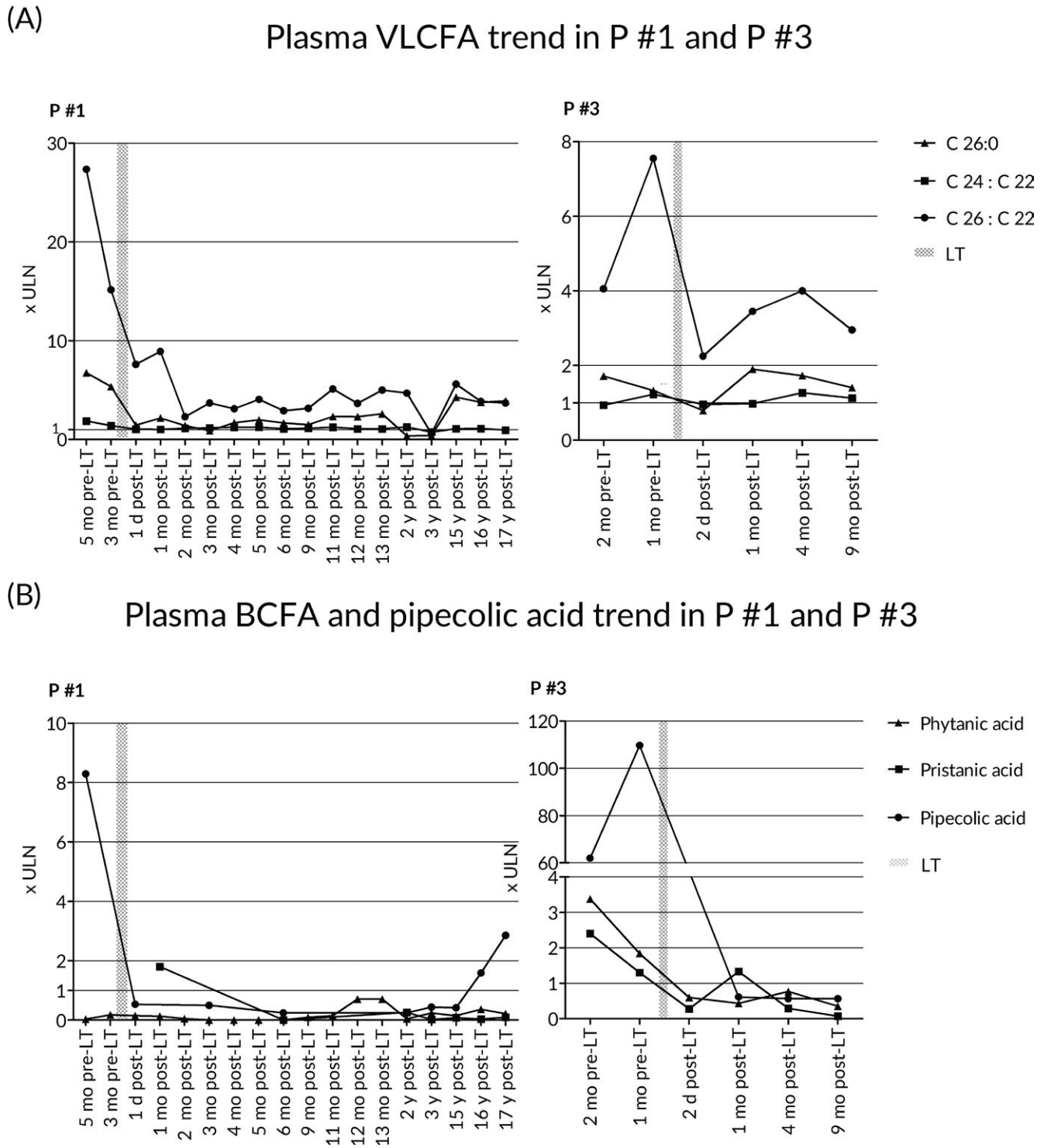

FIGURE 1 Patient 1 and 3's biochemical trend. Plasma VLCFA, BCFA, and pipecolic acid levels (expressed as number of times of the upper limit of the normal); in patient 1 and patient 3. ×ULN, number of times of the upper limit of the normal; LT, liver transplantation; VLCFA, very-long-chain fatty acids; BCFA, branched-chain fatty acids

post-LT hospital stay, metabolic control, and other surgical complications has not been any different from LT performed for other indications. P #1 experienced two episodes of rejection and suffered from biliary stenosis requiring surgical intervention, while the last protocol biopsy conducted at 15 years post-LT showed mild-moderate fibrosis (Metavir 2, Liver Allograft Fibrosis Score 3/9-P2S1C0) without significant inflammation. P #3 neither experienced any rejection episodes nor any other complications. Both are currently managed with the tacrolimus-based immunosuppression regimen.

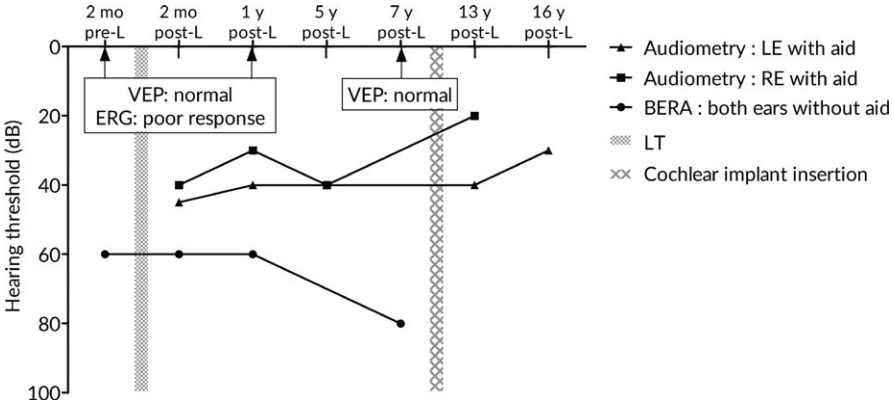

FIGURE 2 Patient 1 hearing thresholds measured by BERA (without aid) or audiometry (with aid). LT, liver transplantation; VEP, visual evoked potentials; ERG, electroretinogram; BERA, brainstem-evoked response audiometry; LE, left ear, RE, right ear

7 | DISCUSSION

This report on the long-term evolution of the first LT for mild ZSD was expected by the metabolic community.[12] We included one additional patient, whose outcome corroborated the benefit of LT on circulating metabolites, clinical outcome, and autonomy acquisition. Both children had received a transplant relatively early in life and before they developed a profound neurological handicap. Consequently, their neurodevelopmental outcomes were better than their older affected siblings who had not been transplanted.

In our experience with three LT for mild ZSD, P #2 died 18 days post-LT after an acute hypotension episode with electrolyte imbalance, which could be compatible with acute adrenal insufficiency. Primary adrenal insufficiency is an underdiagnosed complication in ZSD,[13] and cortisone supplementation should be prescribed to patients with an altered Synacthen® test.[12] This further highlights the need for experienced centers to perform LT in mild ZSD and to manage the affected patients.

Pre-LT phytanic acid level was elevated except in P #1, which can be attributable to a low-phytanic acid diet and his young age (inadequate duration for the accumulation of phytanic acid).[14,15] Phytanic acid was shown to be a toxic metabolite,[5] prompting the adoption of low-phytanic acid diet as a treatment modality.[16] This approach did not result in symptom stabilization or improvement in our patient, as has also been previously reported.[14] Following LT, the phytanic acid levels normalized in all patients as the new allografted liver cleared the toxic metabolite (Figure 1, Table 2). Similar observation was made by the Japanese team that has also recently performed LT for mild ZSD.[17] In the long term, P #1's low-phytanic acid diet became more liberal (ie, she now eats green vegetables, fish, and red meat).

In ZSD, characteristically elevated pristanic and pipecolic acid levels are seen. In vitro pristanic and pipecolic acids were shown to induce oxidative stress in cerebellum and cerebral cortex of young rats,[18-20] which implicates these metabolites to have a neurotoxic effect in ZSD. Remarkably, both normalized after LT and also LCT.[7] The normalization of these metabolite levels could account for the neurodevelopmental benefit that was observed in our patients.

In ZSD, the VLCFA levels are raised due to their inadequate metabolism in the peroxisomes and have a vast range of toxic effects.[21] C26:C22 and C24:C22 ratios showed a decrease post-LT in both our patients, as was also seen by Matsunami et al. In isolation, the C26:0 levels decreased until 15 years post-LT, C24:0 levels decreased, and the C22:0 increased, which resulted in improvement of the C26:C22 and C24:C22 ratios. The new allografted liver is thought to correct the VLCFA metabolism, and this would have resulted in a decrease of C26:0, C24:0, and also of C22:0. This is in contrast to our observation, wherein C26:0 and C24:0 decreased but unexpectedly C22:0 increased. As post-LT tacrolimus is administered, it could possibly affect the VLCFA (C22:0), explaining the above finding, but this aspect is a mere speculation as it is never been evaluated and needs further studies.

C_{27}-bile acid intermediates classically accumulate in ZSD. They were previously shown to be undetectable 2 years post-LT[6] and at last follow-up in P #1. They were not measured in patient #2 and #3. In a recent trial, cholic acid therapy in ZSD without severe liver disease was shown to decrease bile acid intermediates but failed to demonstrate a benefit on the other implicated toxic metabolites. Unfortunately, clinical improvement was not evaluated in this study, given the short duration of follow-up.[22]

Post-LT RBC plasmalogens levels do not draw any clear trend of evolution. They are manufactured in the peroxisomes of bone marrow precursor cells,[23] and thus, no effect would be expected after LT. Thirty years ago, oral plasmalogen supplementation was tried in a few patients with mild ZSD.[24,25] They showed some benefit, but no further study was performed since then.

Limited language and verbal skills are observed in half of the patients surviving into adulthood.[3,26] P #1's verbal skills were acquired in the early post-LT period and subsequently stabilized (Figure 3); 17 years post-LT, P #1 achieved relative social autonomy and can dress herself, eat and travel by herself to school. Her hearing ability stabilized after receiving the cochlear implant and the improvement of nystagmus was remarkable.

There was a clear contrast between the post-LT evolution of P #1 and P #3 in comparison with their older siblings, who followed the natural disease outcome. The 19-year-old elder sister of P #1 exhibited a complete lack of independent living skills to the extent of an inability to walk, along with a total lack of interest and interaction with her surroundings. P #3's elder 7-year-old brother

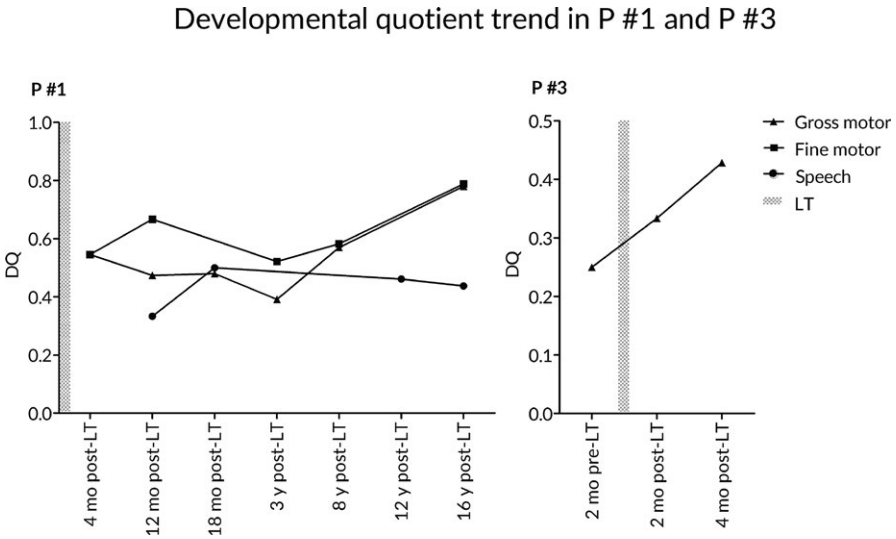

FIGURE 3 Patient 1 and 3 developmental milestone acquisition measured by the developmental quotient. DQ, developmental quotient; LT, liver transplantation

displayed a similar evolution; he is completely bedridden, with a total lack of interest in his surroundings. Nonetheless, intrafamilial phenotypic variability was published previously[27] and this could partially account for the contrast seen in our patients. No genophenotype correlation could be drawn in our patients as the mutations they carry were previously reported in other patients without any clinical information.[28,29] A study on patients with mild-*est* ZSD surviving until adulthood (ie, excluding patients who died before) showed a late normalization of certain metabolites levels in a subset of patients. By extrapolation, it could be proposed that our patients would also have shown biochemical improvement later in life. Given our current limitations of understanding ZSD, wherein we cannot predict the clinical evolution, the above proposition would be the "best case scenario" that can be imagined for any child having ZSD. Unfortunately, by when it would become explicit whether neurological involvement is going to be severe or not, the window of opportunity to perform an LT would have been shut. Furthermore, our patients showed a decrease in toxic metabolites levels just after LT, which cannot be the natural history of the disease, consequently protecting them from the toxicity during the key neurodevelopmental period of childhood. Hence, we speculate that if LT is to be considered, it should be early and, definitely, before the onset of profound neurocognitive impairment.

Moreover, ZSD diagnosis before neurological deficit appears is rendered possible as C26:0-lysophosphatidylcholine level assessment has recently been added to the newborn screening in the United States for the early detection of X-linked adrenoleukodystrophy, a related peroxisomal disorder.[12] Although we and others[17] have achieved significant improvements in this disease usually associated with dismal outcomes, further evaluation is required to strengthen the place of LT as a therapy to modify the natural history of ZSD and to identify children who would most likely benefit from this approach. Among the promising future therapies, adult-derived liver stem/progenitor cells hold significant promise[30] as demonstrated by initial in vitro data.[31]

8 | CONCLUSION

In two patients affected by a mild ZSD, LT induced short-term (9 months of follow-up) and long-term (>17 years of follow-up) metabolic improvement and neurodevelopmental benefits in comparison with their respective affected non-transplanted sibling.

AUTHORS' CONTRIBUTIONS

Tanguy Demaret and Sharat Varma: Contributed equally to this work; Etienne Sokal, and Sharat Varma: Designed the study; Tanguy Demaret: Collected the data; Ronald Wanders: Performed biochemical studies; Tanguy Demaret, Etienne Sokal, and Sharat Varma: Interpreted the data; Tanguy Demaret, and Sharat Varma: Drafted the initial manuscript; Etienne Sokal: Reviewed and revised the manuscript; Xavier Stephenne, Françoise Smets, Isabelle Scheers, Ronald Wanders, and Raymond Reding: Critically reviewed the manuscript; All authors approved the final manuscript for submission.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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