Published in final edited form as:

Am J Med Genet A. 2019 June ; 179(6): 1015–1019. doi:10.1002/ajmg.a.61104.

Improved clinical outcome following liver transplant in patients with ethylmalonic encephalopathy

Allison Tam[1,2,3,†], **Noura Salem AlDhaheri**[1,2,4,†], **Krupa Mysore**[5], **Mary Elizabeth Tessier**[5], **John Goss**[2,6], **Luis A. Fernandez**[7], **Anthony M. D'Alessandro**[7], **Jessica Scott Schwoerer**[8], **Gregory M. Rice**[8], **Sarah H. Elsea**[1], **Fernando Scaglia**[1,2,9]

[1]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas

[2]Department of Molecular and Human Genetics, Texas Children's Hospital, Houston, Texas

[3]Division of Medical Genetics, Department of Pediatrics, University of California San Francisco, San Francisco, California

[4]Department of Pediatrics, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, UAE

[5]Department of Gastroenterology and Hepatology, Texas Children's Hospital, Houston, Texas

[6]Division of Abdominal Transplantation, Baylor College of Medicine, Houston, Texas

[7]Department of Surgery, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

[8]Department of Pediatrics and the Waisman Center, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

[9]BCM-CUHK Center of Medical Genetics, Prince of Wales Hospital, Hong Kong SAR

Abstract

Ethylmalonic encephalopathy (EE) is a rapidly progressive autosomal recessive mitochondrial disease caused by biallelic pathogenic variants in the *ETHE1* gene that encodes the mitochondrial sulfur dioxygenase. It is characterized by neurodevelopmental delay and regression, pyramidal and extrapyramidal signs, recurrent petechiae, chronic diarrhea, and orthostatic acrocyanosis. Laboratory findings include elevated serum levels of lactate and C4-C5 acylcarnitines, and elevated urinary excretion of ethylmalonic acid and C4-C6 acylglycines, notably isobutyrylglycine and 2-methylbutyrylglycine. These findings are attributed to deficiency of the mitochondrial

Correspondence Fernando Scaglia, Department of Molecular and Human Genetics, Baylor College of Medicine/Texas Children's Hospital, 6701 Fannin Street, Suite 1560, Houston, TX 77030. fscaglia@bcm.edu.
[†]Tam and AlDhaheri should be considered joint first authors.

CONFLICT OF INTEREST

Fernando Scaglia receives research support from BioElectron Technologies and Stealth Therapeutics; and is an investigator in the North American Mitochondrial Disease Consortium.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Informed Consent

Genetic analysis was performed after obtaining a written informed consent from both parents. Consent to publish clinical data of the patients was obtained from both parents of the minors.

sulfur dioxygenase resulting in toxic accumulation of hydrogen sulfide metabolites in vascular endothelium and mucosal cells of the large intestine. Medical management has thus far been directed toward decreasing the accumulation of hydrogen sulfide metabolites using a combination of metronidazole and *N*-acetylcysteine. More recently, orthotopic liver transplant (OLT) has been reported as a new therapeutic option for EE. Here, we report two additional cases of EE who achieved psychomotor developmental improvement after 7- and 22-months following OLT. The second case serves as the longest developmental outcome follow-up reported, thus far, following OLT for EE. This report provides additional evidence to validate OLT as a promising therapeutic approach for what was considered to be a fatal disease.

Keywords

ETHE1 ; ethylmalonic encephalopathy; hydrogen sulfide toxicity; mitochondrial sulfur dioxygenase; orthotopic liver transplant

1 | INTRODUCTION

Ethylmalonic encephalopathy (EE) is an autosomal recessive disorder caused by biallelic pathogenic variants in *ETHE1* (Tiranti et al., 2004, 2006). *ETHE1* (OMIM: 608451) encodes a mitochondrial sulfur dioxygenase, which plays an important role in hydrogen sulfide (H_2S) detoxification (Tiranti et al., 2009). EE is characterized by neurodevelopmental delay and regression, prominent pyramidal and extrapyramidal signs, recurrent petechiae, chronic diarrhea, and orthostatic acrocyanosis (Burlina et al., 1991, 1994; Tiranti et al., 2004). Neuroradiological findings typically include bilateral necrotic lesions in the deep gray matter. Laboratory findings can include elevated serum levels of lactate and C4-C5 acylcarnitines and elevated urinary excretion of ethylmalonic acid and C4-C6 acylglycines, notably isobutyrylglycine and 2-methylbutyrylglycine (Burlina et al., 1991, 1994; Drousiotou et al., 2011; Tiranti et al., 2004). EE was first described in 1991 by Burlina et al. (1991), and most reported patients have been of Mediterranean and Arabic descent (Tiranti et al., 2004, 2006).

Deficiency of the mitochondrial sulfur dioxygenase results in accumulation of H_2S and its derivative thiosulfate, and H_2S toxicity is thought to be the driving pathogenic mechanism in EE (Tiranti et al., 2009). High concentrations of H_2S induce damage to vascular endothelial cells and mucosal cells of the large intestine, which may explain the diffuse vascular damage most evident in the brain, gastrointestinal tract (GI), and peripheral vessels (Di Meo et al., 2011; Giordano et al., 2012; Tiranti et al., 2009) and the corresponding clinical manifestations including necrotic brain lesions, chronic diarrhea, petechial purpura, and orthostatic acrocyanosis. High concentration of H_2S inhibits cytochrome *c* oxidase (COX) activity in muscle, brain, and colonic mucosa, which disrupts mitochondrial respiration resulting in elevated serum lactic acid and clinical manifestations of mitochondrial disease. It also inhibits the activity of short-chain acyl-CoA dehydrogenase, which consequently leads to elevated serum C4-C5 acylcarnitines, and elevated urinary excretion of ethylmalonic acid and C4-C6 acylglycines, as observed in these patients (Di Meo et al., 2011; Tiranti et al., 2009).

EE is an invariably fatal disorder with progressive clinical deterioration and mortality typically in the first few years of life (Dionisi-Vici et al., 2016; Martinelli et al., 2012). Dionisi-Vici et al. conducted orthotopic liver transplant (OLT) in a 9-months old infant with EE with the rationale of using the donated liver to filter the blood from the toxic H_2S coming mostly from the GI tract. They observed striking neurological improvements and reversal of biochemical abnormalities and, thus claimed that OLT may be a viable therapeutic option for EE (Dionisi-Vici et al., 2016). Here, we report two patients with EE who underwent OLT at ages 19 and 13 months, respectively, with clinical and biochemical improvements thereafter. To our knowledge, this is the second published report of OLT as a treatment for EE since the original report.

1.1 | Case 1

Patient 1 was a 13-month-old girl born to consanguineous parents after an uncomplicated pregnancy and delivery at full term with normal growth parameters. Newborn screen (NBS) showed borderline elevated C4 at 1.41 μmol/L (cutoff for borderline is 1.3 μmol/L). She had daily diarrhea since birth and petechial rash in the face and extremities since 4 months of age. Global developmental delay became evident at age 6 months. MRI brain at age 9 months revealed bilateral basal ganglia and corona radiata bright signals associated with dilated extra-axial CSF spaces. She started cooing at 7 months and reaching for objects at 10 months. When she was evaluated at 13 months, she had poor head control, not pushing herself up on forearms and not rolling over. She was not transferring objects and not babbling. At 13 months, her weight and height were both below first percentile and had diffuse hypotonia, extensive petechial rash, and acrocyanosis. Acylcarnitine profile revealed elevated C4 at 2.31 μmol/L (nl < 0.60) and C5 at 0.59 μmol/L (nl < 0.50). Urine organic acid profile revealed elevated ethylmalonic acid. Metabolomic profile showed elevation of ethylmalonate (*Z*-score 4.93) and methylsuccinate (*Z*-score 2.84). Urine acylglycine and metabolomic profiles are summarized in Tables 1 and 2. She also had evidence of lactic acidosis (4.2 mmol/L). She had no evidence of hyperammonemia with a value of 14 μmol/L. The patient had clinical and biochemical findings consistent with EE. Molecular analysis of *ETHE1* showed a homozygous deletion of exon 4. This deletion was previously reported in patients with EE (Drousiotou et al., 2011).

A combined regimen of metronidazole 30 mg/kg/day and *N*-acetylcysteine (NAC) 105 mg/kg/day divided into three daily doses was initiated. Following initiation of medical therapy with metronidazole and NAC, C4 decreased from baseline but remained elevated, and C5 normalized. As summarized in Table 2, metabolomic profile showed slight decrease in ethylmalonate and methylsuccinate after 3-month of medical management only. Her weight drastically improved after initiation of medical management, from *Z*-score −3.8 at time of initial evaluation to *Z*-score of −2.2 and −2.0 at 2 and 5 months, respectively. Her diarrhea and acrocyanosis had improved, but no major improvements were noticed in her development.

At 19-month, our patient received OLT from a deceased donor. Despite few postsurgical and medical complications, including cytomegalovirus, adenovirus infections, and bacteremia, brain MRI did not show significant changes from her baseline. Low carnitine levels were

found, and therefore, intravenous carnitine was started at 100 mg/kg/day. Metronidazole and NAC were continued. Ammonia level remained normal with a value of 26 μmol/L. She recovered well and was discharged on postoperative day 51. Lactate level normalized after transplant. C4 decreased but remained elevated and C5 normalized. Urine acylglycine and metabolomic profiles showed drastic decrease in several metabolites from baseline. Pre- and post-transplant profiles are summarized in Tables 1 and 2.

Developmentally, post-transplant, our patient's social interaction and language have drastically improved. She became more interactive, started babbling and was able to grab and reach out for objects. At 26 months of age (7-months post-transplant), she showed further developmental improvement. She sat unsupported and started to roll over. Her formal developmental assessment at 28 months (9-months post-transplant) showed: gross motor abilities between 3 and 5 months (Gesell Developmental Schedules), visual-motor problem solving abilities at 8–2/3 months (Cognitive Adaptive Test, Capute Scales), and speech and language abilities at 8–9 months (Clinical Linguistic and Auditory Milestone, Capute Scales).

1.2 | Case 2

Patient 2 was born to consanguineous parents at term following an uncomplicated pregnancy. He was identified as being at risk for EE due to the diagnosis of an affected sibling who died at 2 years of age following a severe episode of encephalopathy associated with influenza. NBS showed elevated C4 and C5. Plasma acylcarnitines showed elevated C4 at 2.17 μmol/L (nl < 0.62) and C5 at 0.77 μmol/L (nl < 0.30). Initial urine organic acid analysis showed marked elevation of ethylmalonic acid 177 mg/g Cr (nl < 17) and 2-methylsuccinic acid 18.9 mg/g Cr (nl < 13.8). Urine acylglycines showed elevation in isobutyrylglycine 11.53 mg/g Cr (nl < 11) and borderline elevation in 2-methylbutyrylglycine 7.39 mg/g Cr (nl 0.3–7.5) (Table 1). He has no evidence of hyperammonemia with value of 36 μmol/L (nl 16–68). Molecular testing revealed a homozygous known pathogenic variant in *ETHE1* (c.487C > T, p.R163W) at 8 weeks of age (Tiranti et al., 2004). Metronidazole at 30 mg/kg/day and NAC at 100 mg/kg/day were started. Developmentally, he had social smile and laughter but otherwise had global developmental delay with profound hypotonia and required gastrostomy tube placement in the newborn period. MRI of the brain was not performed at the time of diagnosis. Our patient underwent OLT at age 13 months without major complications. Metronidazole and NAC were continued after liver transplantation.

Following medical treatment, ethylmalonate improved from 177 mg/g Cr to 141 mg/g Cr (nl < 17). However, following transplantation, metabolite levels decreased markedly; ethylmalonic acid was 32.17 mg/g Cr (nl < 20.2), isobutyrylglycine was 3.01 mg/g Cr (nl < 11) and 2-methylsuccinic acid was 4.71 mg/g Cr (nl < 13.8). Plasma acylcarnitines showed decreased C4 of 0.54 umol/L (nl < 0.50) and C5 of 0.04 umol/L (nl < 0.07). Ammonia level post-transplant remained unremarkable with values ranging between 21 and 65 μmol/L (nl 16–68). Development assessment at 15 months of age (2 months post liver transplant) showed profound hypotonia, but he was able to sit independently and attempted to crawl. He showed great social interaction and started babbling.

He made slow developmental progress until 20 months of age when he had fever with gastroenteritis, which precipitated an encephalopathic crisis and a metabolic stroke requiring intubation. An MRI of the brain showed multiple areas of acute and subacute infarcts scattered in bilateral cerebellar white matter, bilateral striatum, callosal genu, and splenium. MR spectroscopy showed elevated lactate in the basal ganglia. His ethylmalonic acid increased to 88.92 mg/g Cr (nl < 20.2). He slowly recovered but had regression of developmental skills and developed spastic quadriplegia. Now, at 35 months of age, he has had no other encephalopathic episodes and is making slow developmental progress. He is unable to stand but can sit without support and can commando crawl. He reaches objects but struggles with grasp. He has five words and follows simple one-step commands.

2 | DISCUSSION

EE is a fatal, progressive, multisystem recessive disorder of variable onset and severity; however, patients typically present in early infancy or childhood (Tiranti et al., 2004). Elevated C4 and C5 acylcarnitines may be detected if they are assessed by NBS, as they were in both patients herein presented and as previously reported in the literature (Boyer et al., 2018). Theoretically, if EE is potentially diagnosed before the onset of neonatal symptoms, early treatment may effectively alter the disease course and improve clinical outcome.

The *Ethe1*$^{-/-}$ mouse model recapitulates the clinical and biochemical features seen in human patients with EE, including growth arrest, reduced motor activity, decreased lifespan, elevated lactate, C4 and C5 acylcarnitines, increased urinary excretion of ethylmalonic acid, and the accumulation of sulfide in tissues including brain, liver, muscle, and colonic mucosa (Tiranti et al., 2009). Morphologic evidence of diffuse vascular damages particularly in the brain and colonic mucosa, where there are increased sulfide levels, have been shown in an autopsy performed on an EE patient, as well as in *Ethe1*$^{-/-}$ mouse model (Giordano et al., 2012). Understanding the pathogenesis of EE and the availability of the *Ethe1*$^{-/-}$ mouse model have led to the development of therapeutic approaches aimed at decreasing the accumulation of H_2S.

Metronidazole and NAC are off-label medications used to decrease H_2S accumulation in EE patients. Major source of H_2S in mammals is the anaerobic bacterial flora of the large intestine (Flannigan, McCoy, & Wallace, 2011). Metronidazole is an antibiotic effective against anaerobic bacteria used to decrease bacterial production of H_2S. NAC is a cell permeable precursor of glutathione, which can accept sulfur atoms from H_2S and form nontoxic compounds, and therefore could neutralize toxic H_2S. A combination therapy of metronidazole and NAC was tested in *Ethe1*$^{-/-}$ mouse model with observed prolonged survival and increased COX activity in the large intestine. Daily combination therapy of oral metronidazole and NAC were subsequently tested in EE patients, resulting in improved clinical symptoms including diarrhea, petechiae, acrocyanosis, and abnormal tone. Furthermore, treated patients have decreased plasma ethylmalonic acid and thiosulfate (Viscomi et al., 2010). Given these results, metronidazole and NAC were started at diagnosis and continued after liver transplantation in both patients herein presented.

Di Meo et al. speculated that OLT could be a therapeutic option for EE patients based on positive outcomes in the *Ethe1*$^{-/-}$ mouse model that had liver-specific adeno-associated virus-medicated expression of human wild-type *ETHE1* (Di Meo et al., 2012). They reasoned that the liver can act as a filter to detoxify most of the blood from the gastrointestinal tract in which toxic H_2S is produced by anaerobic bacteria. In 2016, Dionisi-Vici et al. reported an EE patient who underwent OLT at 9 months of age. Striking neurological improvement in psychomotor development and dramatic reversion of biochemical abnormalities was observed 8 months post-transplant (Dionisi-Vici et al., 2016). Therefore, we decided to proceed with OLT for our patients. Patient 1 showed clinical improvement specifically developmental progress. Despite some post-transplant complications, she did not show evidence of neurological worsening on brain MRI. This is possibly because she was still in ICU post-transplant and was receiving parenteral nutrition therapy, which might have prevented catabolism during her acute infection. At the time of this report, she continued to show developmental progress. Patient 2 showed developmental progress after transplant, however, had an encephalopathic crisis with metabolic stroke in the setting of acute viral illness long after his transplant. Nevertheless, he recovered partially and made more developmental progress afterwards. Now, at 35 months he shows language development with five words, which is not typical for this disorder. To our knowledge, this is the longest developmental outcome follow-up post-transplant for EE reported thus far.

Interestingly, untargeted metabolomic profile in Patient 1 demonstrated persistent abnormal metabolites including ethylmalonate and isobutyrylcarnitine even after OLT (Table 2). This indicates that despite transplant, EE patients might still be at risk for vascular complications including neurologic insults in the setting of an infection or other stressors. Therefore, post-transplant, patients may benefit from continuation of NAC, carnitine, and metronidazole.

Inborn metabolic disease is one of the most common indications for OLT accounting for about 20% of pediatric cases (Mc Kiernan, 2017). Many of these disorders have toxic intermediary metabolites that can be corrected by a normal liver. EE fits in this group of disorders. OLT was demonstrated to be a potential lifesaving treatment for patients with EE by Dionisi-Vici et al. and in our report. Furthermore, there is the potential of identifying patients with EE in infancy through NBS and to initiate treatment early in the disease course. The observations of clinical improvement in our patients who underwent liver transplantation serve to provide additional evidence to “validate this promising approach as standard of care for patients with EE” as suggested previously (Boyer et al., 2018) given the devastating natural history of EE and the lack of superior therapeutic options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

The authors would like to thank the patients, their families, and all physicians involved in their care. AT was supported by NIH training grant (T32GM07526-40).

REFERENCES

Boyer M, Sowa M, Di Meo I, Eftekharian S, Steenari MR, Tiranti V, & Abdenur JE (2018). Response to medical and a novel dietary treatment in newborn screen identified patients with ethylmalonic encephalopathy. Molecular Genetics and Metabolism, 124, 57–63. 10.1016/j.ymgme.2018.02.008 [PubMed: 29526615]

Burlina AB, Dionisi-Vici C, Bennett MJ, Gibson KM, Servidei S, Bertini E, … Rinaldo P (1994). A new syndrome with ethylmalonic aciduria and normal fatty acid oxidation in fibroblasts. Journal of Pediatrics, 124(1), 79–86. 10.1016/S0022-3476(94)70257-8 [PubMed: 8283379]

Burlina AB, Zacchello F, Dionisi-Vici C, Bertini E, Sabetta G, Bennet MJ, … Rinaldo P (1991). New clinical phenotype of branched-chain acyl-CoA oxidation defect. The Lancet, 8781(338), 1522–1523. 10.1016/0140-6736(91)92338-3

Di Meo I, Auricchio A, Lamperti C, Burlina A, Viscomi C, & Zeviani M (2012). Effective AAV-mediated gene therapy in a mouse model of ethylmalonic encephalopathy. EMBO Molecular Medicine, 4(9), 1008–1014. 10.1002/emmm.201201433 [PubMed: 22903887]

Di Meo I, Fagiolari G, Prelle A, Viscomi C, Zeviani M, & Tiranti V (2011). Chronic exposure to sulfide causes accelerated degradation of cytochrome c oxidase in ethylmalonic encephalopathy. Antioxidants & Redox Signaling, 15(2), 353–362. 10.1089/ars.2010. [PubMed: 20812865]

Dionisi-Vici C, Diodato D, Torre G, Picca S, Pariante R, Giuseppe Picardo S, … De Goyet JDV (2016). Liver transplant in ethylmalonic encephalopathy: A new treatment for an otherwise fatal disease. Brain, 139(4), 1045–1051. 10.1093/brain/aww013 [PubMed: 26917598]

Drousiotou A, Dimeo I, Mineri R, Georgiou T, Stylianidou G, & Tiranti V (2011). Ethylmalonic encephalopathy: Application of improved biochemical and molecular diagnostic approaches. Clinical Genetics, 79(4), 385–390. 10.1111/j.1399-0004.2010.01457.x [PubMed: 20528888]

Flannigan KL, McCoy KD, & Wallace JL (2011). Eukaryotic and prokaryotic contributions to colonic hydrogen sulfide synthesis. AJP: Gastrointestinal and Liver Physiology, 301(1), G188–G193. 10.1152/ajpgi.00105.2011

Giordano C, Viscomi C, Orlandi M, Papoff P, Spalice A, Burlina A, … Zeviani M (2012). Morphologic evidence of diffuse vascular damage in human and in the experimental model of ethylmalonic encephalopathy. Journal of Inherited Metabolic Disease, 35(3), 451–458. 10.1007/s10545-011-9408-3 [PubMed: 22020834]

Martinelli D, Catteruccia M, Piemonte F, Pastore A, Tozzi G, Dionisi-Vici C, … Miller G (2012). EPI-743 reverses the progression of the pediatric mitochondrial disease-genetically defined Leigh syndrome. Molecular Genetics and Metabolism, 107(3), 383–388. 10.1016/j.ymgme.2012.09.007 [PubMed: 23010433]

Mc Kiernan PJ (2017). Recent advances in liver transplantation for metabolic disease. Journal of Inherited Metabolic Disease, 40(4), 491–495. 10.1007/s10545-017-0020-z [PubMed: 28168361]

Miller MJ, Kennedy AD, Eckhart AD, Burrage LC, Wulff JE, Miller LAD, … Elsea SH (2015). Erratum to: Untargeted metabolomic analysis for the clinical screening of inborn errors of metabolism. Journal of Inherited Metabolic Disease, 38, 1029–1039. 10.1007/s10545-016-9944-y [PubMed: 25875217]

Tiranti V, Briem E, Lamantea E, Mineri R, Papaleo E, De Gioia L, … Zeviani M (2006). ETHE1 mutations are specific to ethylmalonic encephalopathy. Journal of Medical Genetics, 43(4), 340–346. 10.1136/jmg.2005.036210 [PubMed: 16183799]

Tiranti V, D'Adamo P, Briem E, Ferrari G, Mineri R, Lamantea E, … Zeviani M (2004). Ethylmalonic encephalopathy is caused by mutations in ETHE1, a gene encoding a mitochondrial matrix protein. American Journal of Human Genetics, 74(2), 239–252. 10.1086/381653 [PubMed: 14732903]

Tiranti V, Viscomi C, Hildebrandt T, Di Meo I, Mineri R, Tiveron C, … Zeviani M (2009). Loss of ETHE1, a mitochondrial dioxygenase, causes fatal sulfide toxicity in ethylmalonic encephalopathy. Nature Medicine, 15(2), 200–205. 10.1038/nm.1907

Viscomi C, Burlina AB, Dweikat I, Savoiardo M, Lamperti C, Hildebrandt T, … Zeviani M (2010). Combined treatment with oral metronidazole and N-acetylcysteine is effective in ethylmalonic encephalopathy. Nature Medicine, 16(8), 869–871. 10.1038/nm.2188

TABLE 1

Urine acylglycine profile pre- and post-transplant

	Patient 1 (mmol/mole Cr)		Patient 2 (mg/g Cr)	
Urine acylglycine	**At diagnosis**	**After transplant**	**At diagnosis**	**After transplant**
Isobutyrylglycine	750.8 (<9)	12.6 (<9)	11.53 (<11)	3.01 (<11)
Isovalerylglycine	<0.2 (0–10)	18 (0–10)	22.61 (0.3–14.3)	5.37 (0.3–14.3)
2-Methylbutyrylglycine	131.8 (<5)	3.2 (<5)	7.39 (0.3–7.5)	4.06 (0.3–7.5)

Marked decrease in metabolites was observed 5-months post-transplant for Patient 1. Patient 2 had borderline elevations at diagnosis with normalized values post-transplant. Normal reference values are indicated within parenthesis.

TABLE 2

Summary of metabolomic profile pre- and post-transplant

Metabolic analytes	At time of evaluation	3 months after medications initiated	5 months after medications initiated	1 month post-OLT	5 months post-OLT	7 months post-OLT
Ethylmalonate	4.93	4.47	7.44	4.96	5.22	5.10
Butyrylcarnitine	2.95	3.41	5.08	4.99	5.01	4.89
Isobutyrylcarnitine	3.39	3.26	4.43	2.14	3.72	3.40
Isovalerylcarnitine	3.06	3.14	4.1	1.94	3.89	3.61
Glutaroylcarnitine	3.48	3.04	3.66	0.25	Not detected	Not detected
2-Methylbutyroylcarnitine	2.88	2.69	3.77	1.72	Not detected	Not detected
2-Methylsuccinate	2.84	2.39	5.15	−0.95	1.39	2.24

Metabolomic profile results for Patient 1 at different time points including: at the time of evaluation at age 13 months; at 3 months and 5 months after NAC and metronidazole were initiated; at 1 month, 5 months, and 7 months post-liver transplant. Numerical values represent *Z*-scores of different metabolic analyte levels in plasma. Metabolomic analysis was performed at Baylor Genetics Laboratory (www.BaylorGenetics.com) (Miller et al., 2015).

Am J Med Genet A. Author manuscript; available in PMC 2023 January 24.