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RESEARCH REPORT

Mitochondrial Encephalopathy and Transient 3-Methylglutaconic Aciduria in ECHS1 Deficiency: Long-Term Follow-Up

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Abstract We report the major diagnostic challenge in a female patient with signs and symptoms suggestive of an early-onset mitochondrial encephalopathy. Motor and cognitive development was severely delayed and brain MRI showed signal abnormalities in the putamen and caudate nuclei. Metabolic abnormalities included 3-methylglutaconic aciduria and elevated lactate levels in plasma and cerebrospinal fluid, but were transient. Whole exome sequencing at the age of 25 years finally revealed compound heterozygous mutations c.[229G>C];[563C>T], p.[Glu77Gln];[Ala188Val] in the *ECHS1* gene. Activity of short-chain enoyl-CoA hydratase, a mitochondrial enzyme encoded by the *ECHS1* gene, was markedly decreased in lymphocytes. Retrospective urine analysis confirms that elevated levels of *S*-(2-carboxypropyl)cysteamine, *S*-(2-carboxypropyl)cysteine, and *N*-acetyl-*S*-(2-carboxypropyl)cysteine can be a diagnostic clue in the disease spectrum of *ECHS1* mutations.

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Introduction

Short-chain enoyl-CoA hydratase (SCEH, also known as crotonase, EC 4.2.1.17), which is encoded by the *ECHS1* gene (OMIM no. 602292), has a broad substrate specificity and is involved in valine and isoleucine metabolism as well as in mitochondrial β-oxidation of short-chain and medium-chain fatty acids (Wanders et al. 2012). Deficiency of this mitochondrial enzyme has been associated with an encephalopathy similar to Leigh syndrome, in some accompanied by cardiac defects, optic abnormalities, epilepsy, and paroxysmal exercise-induced dystonia. The reported patients show various symptoms and biochemical abnormalities (Peters et al. 2014; Ferdinandusse et al. 2015; Haack et al. 2015; Sakai et al. 2015; Tetreault et al. 2015; Yamada et al. 2015; Ganetzky et al. 2016; Nair et al. 2016; Olgiati et al. 2016; Bedoyan et al. 2017; Al Mutairi et al. 2017; Mahajan et al. 2017).

Here, we report the severe neurological course of a 26-year-old female patient with transient metabolic abnormalities, including 3-methylglutaconic aciduria and elevated lactate levels in plasma and cerebrospinal fluid (CSF). The patient had compound heterozygous mutations, c.[229G>C];[563C>T], p.[Glu77Gln];[Ala188Val] (the latter being novel) in the *ECHS1* gene.

Case Report

The female patient is the first child of non-consanguineous Dutch parents who was born after an uncomplicated pregnancy and delivery with a birth weight of 2.81 kg (10th percentile). The presenting symptom was wandering eye movements at 6 weeks of age with a horizontal

nystagmus. Although ophthalmological examination, electroretinography, and visual evoked potentials were normal at first, optical atrophy was noted at the age of 4 years with a visual acuity of 20/100 Snellen equivalent.

Maximum motor development was achieved at 3 months of age with head balance and grasping near objects. Choreoathetosis progressed until the age of 4 but has slowly been ameliorating since. Cognitive development has remained limited to laughing and babbling. To date, at 26 years of age, she shows a spastic tetraparesis and contractures of all major joints with almost no voluntary movements and dystonia during excitement. Visual acuity has diminished to inconsistent light perception. Hearing seems to be intact. Heart ultrasound and an ECG were normal at the age of 20 months. No clinical symptoms and signs of cardiac disease have developed since.

Brain MRI showed mild dilatation of the ventricles with bilateral signal abnormalities on T2-weighted images in the putamen and caudate nuclei at 1 year of age. At the age of 4, atrophy was generalized including basal ganglia and vermis cerebelli superior with signal abnormalities that had progressed to the globi pallidi. No lactate peak was seen on MRS. At 12 years of age atrophy had progressed even further, the corpus callosum was thin, and myelination was delayed (Fig. 1a–i). Repeated EEGs showed no epileptiform activity.

Lactate levels in blood (1.6–4.9 mmol/L; reference range (RR): 0–2.0 mmol/L) were elevated until the age of 7 years, while pyruvate levels were normal. Lactate levels in cerebrospinal fluid (CSF) were also repeatedly elevated (3.2–4.4 mmol/L; RR: 0–2.3 mmol/L) in the first 5 years of life with a marginally elevated pyruvate level (142 µmol/L; RR: 0–130 µmol/L). Analysis of organic acids in urine revealed persistent mild elevations of 3-methylglutaconic acid (22–34 µmol/mmol creatinine; RR: 0–19 µmol/mmol creatinine) until 5 years of age. Levels of 3-methylglutaric acid were slightly increased (7 µmol/mmol creatinine; RR: 0.9–4.5 µmol/mmol creatinine) when the girl was 2 years old and normalized afterwards. Additional organic acid analysis in CSF showed an increase in 3-hydroxyisovaleric acid (15 µmol/L, RR: 1–4 µmol/L) at 2 years of age. This metabolite was also elevated in urine upon leucine-loading (100 mg/kg). Urinary analysis of amino acids was repeatedly normal. Biotinidase activity level in plasma, glutaryl-CoA-dehydrogenase activity in lymphocytes, and 3-methylglutaconyl CoA hydratase activity in fibroblasts were all normal. Holocarboxylase synthetase deficiency was excluded with fibroblast enzyme analysis. A muscle biopsy at 2 years of age revealed no abnormalities in oxidative phosphorylation. Strikingly, even though this patient was severely neurologically affected at 23 years, metabolic profiling, including amino acids, acylcarnitines, and organic acids was normal.

Whole exome sequencing (WES) at 25 years of age revealed compound heterozygous mutations c.[229G>C]; [563C>T], p.[Glu77Gln];[Ala188Val] in the *ECHS1* gene. Mutation analysis by WES confirmed maternal inheritance of c.[229G>C], p.[Glu77Gln] and paternal inheritance of c.[563C>T], p.[Ala188Val]. Activity of SCEH was markedly decreased in lymphocytes (<31 nmol/(min.mg); RR: 101–218 nmol/(min.mg)). Retrospective analysis of metabolites known to be elevated in SCEH deficiency in urine (Peters et al. 2014) showed increased levels of *S*-(2-carboxypropyl)cysteamine, *S*-(2-carboxypropyl)cysteine, and *N*-acetyl-*S*-(2-carboxypropyl)cysteine in our patient (Fig. 1j).

Discussion

The progressive psychomotor retardation, mild 3-methylglutaconic aciduria, and elevated lactate levels in plasma and CSF were highly suggestive for a mitochondrial encephalopathy, which was supported by bilateral signal abnormalities in the basal ganglia on MRI. The increased urinary excretion of 3-methylglutaconic acid was considered an important diagnostic clue, but a muscle biopsy, biotinidase activity level in plasma, glutaryl-CoA-dehydrogenase activity in lymphocytes, and 3-methylglutaconyl CoA hydratase activity in fibroblasts were all normal. In lack of an identified causative disorder, the diagnosis remained unspecified 3-methylglutaconic aciduria for years.

Surprisingly, despite the severe neurological clinical picture, metabolite abnormalities decreased and almost normalized as she got older. Finally, at 25 years of age WES revealed mutations in the *ECHS1* gene, with concomitant decrease in SCEH activity in lymphocytes.

The evolution of the phenotype in this patient highlights the major diagnostic challenge clinicians can face in the diagnosis of the newly recognized disease spectrum of *ECHS1* mutations. The differential diagnosis of mild 3-methylglutaconic aciduria is long and diverse. This transient biochemical abnormality probably was aspecific and due to mitochondrial dysfunction in general (Wortmann et al. 2013). However, in patients with an early-onset severe mitochondrial encephalopathy and absent differentiating biochemical abnormalities, cysteamine/cysteine derivatives should be measured in urine as elevated levels of *S*-(2-carboxypropyl)cysteamine, *S*-(2-carboxypropyl)cysteine, and *N*-acetyl-*S*-(2-carboxypropyl)cysteine can be a diagnostic clue. The urinary levels in our patient were similar to previously reported cases (Peters et al. 2014; Ferdinandusse et al. 2015; Yamada et al. 2015; Olgiati et al. 2016), but not as high as in a severely affected patient that was previously described by Ferdinandusse et al. (2015) (Fig. 1j).

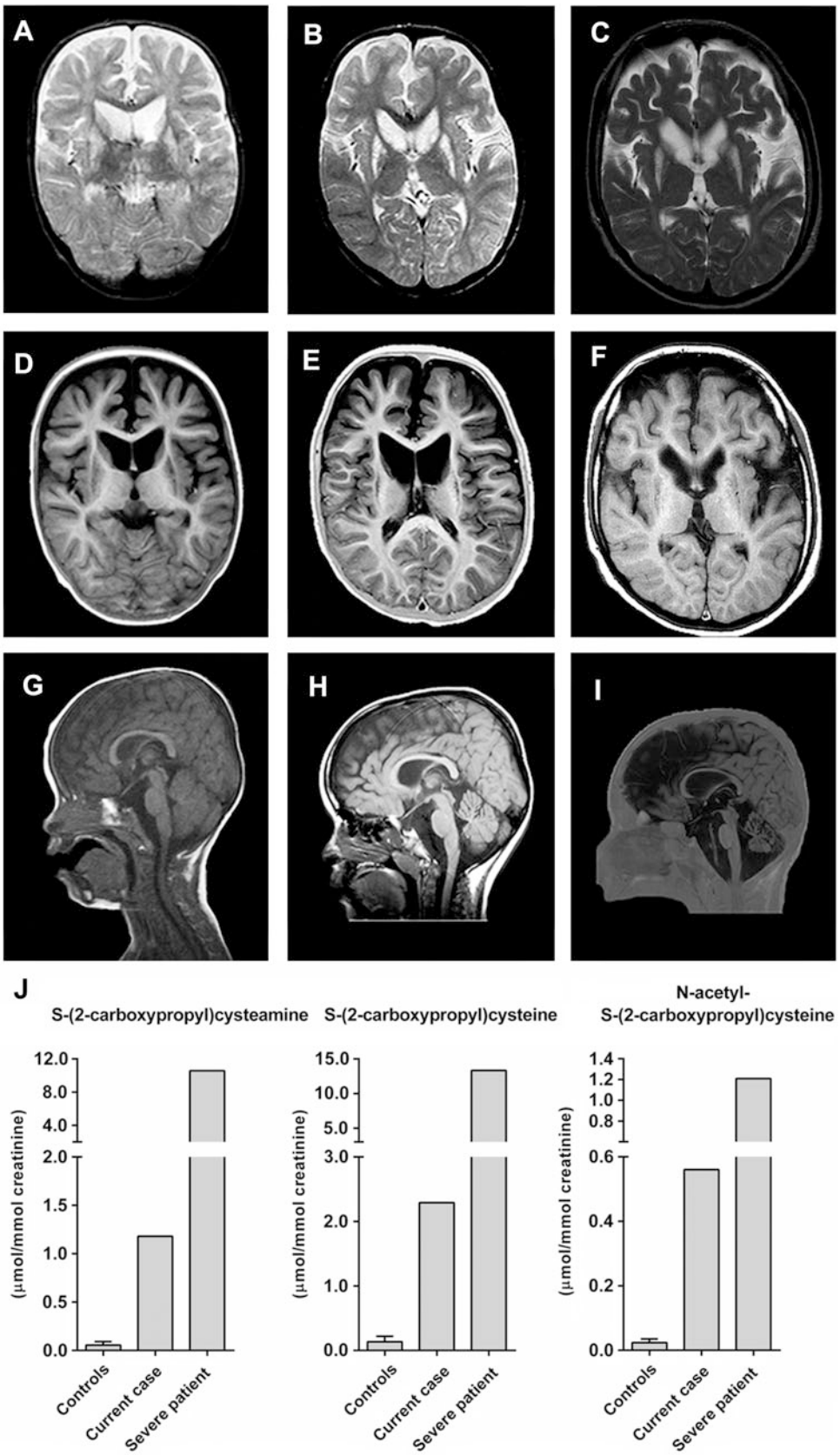

Fig. 1 Brain MRI at age 1, 4, 12 years and metabolite analysis. (**a**, **d**, **g**) Brain MRI at age 1 year. (**b**, **e**, **h**) Brain MRI at age 4 years. (**c**, **f**, **i**) Brain MRI at age 12 years. (**a**–**c**) Axial T2-weighted images. (**d**–**f**) Axial T1-weighted images. (**g**–**i**) Sagittal T1-weighted images.

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Take-Home Message

Elevated levels of *S*-(2-carboxypropyl)cysteamine, *S*-(2-carboxypropyl)cysteine, and *N*-acetyl-*S*-(2-carboxypropyl) cysteine can be a diagnostic clue towards the disease spectrum of *ECHS1* mutations in patients with an early-onset and severe mitochondrial encephalopathy who may survive into adulthood and have transient metabolic abnormalities including 3-methylglutaconic aciduria and elevated lactate levels in plasma and cerebrospinal fluid.

Contributions of Individual Authors

Irene C. Huffnagel: study design, data interpretation, writing manuscript.

Dr. Redeker: analysis and interpretation of genomic array data, critical revision of manuscript for intellectual content.

Dr. Reneman: MRI analysis, critical revision of manuscript for intellectual content.

Dr. Vaz: metabolite analysis, data analysis and interpretation, critical revision of manuscript for intellectual content.

Dr. Ferdinandusse: metabolite analysis, data analysis and interpretation, critical revision of manuscript for intellectual content.

Prof. Dr. Poll-The: study concept, design and supervision, patient care, data interpretation, writing manuscript.

Article Guarantor

Prof Dr. Bwee Tien Poll-The, MD, PhD (corresponding author).

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Compliance with Ethics Guidelines

Conflict of Interest

Irene C. Huffnagel, Egbert J. W. Redeker, Liesbeth Reneman, Frédéric M. Vaz, Sacha Ferdinandusse, and Bwee Tien Poll-The declare that they have no conflict of interest.

Ethics Approval

Not applicable.

Patient Consent Statement

Informed consent was obtained and available upon request.

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Fig. 1 (continued) Initial signal abnormalities are limited to the putamen and caudate nuclei, but progress to the globi pallidi. Atrophy is more generalized at follow-up, including involvement of the vermis cerebelli. (**j**) Levels of *S*-(2-carboxypropyl)cysteamine, *S*-(2-carboxypropyl)cysteine, and *N*-acetyl-*S*-(2-carboxypropyl)cysteine in urine measured by tandem mass spectrometry at 23 years of age compared to five healthy controls and one of the severe *ECHS1* cases published by Ferdinandusse et al. (2015)

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