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IMAGES IN METABOLIC MEDICINE

Unique presentation of cutis laxa with Leigh-like syndrome due to *ECHS1* deficiency

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Abstract Clinical finding of cutis laxa, characterized by wrinkled, redundant, sagging, nonelastic skin, is of growing significance due to its occurrence in several different inborn errors of metabolism (IEM). Metabolic cutis laxa results from Menkes syndrome, caused by a defect in the ATPase copper transporting alpha (ATP7A) gene; congenital disorders of glycosylation due to mutations in subunit 7 of the component of oligomeric Golgi (COG7)–congenital disorders of glycosylation (CDG) complex; combined disorder of N- and O-linked glycosylation, due to mutations in ATPase H+ transporting V0 subunit a2 (ATP6VOA2) gene; pyrroline-5-carboxylate reductase 1 deficiency; pyrroline-5-carboxylate synthase deficiency; macrocephaly, alopecia, cutis laxa, and scoliosis (MACS) syndrome, due to Ras and Rab interactor 2 (RIN2) mutations; transaldolase deficiency caused by mutations in the transaldolase 1 (TALDO1) gene; Gerodermia osteodysplastica due to mutations in the golgin, RAB6-interacting (GORAB or SCYL1BP1) gene; and mitogen-activated pathway (MAP) kinase defects, caused by mutations in several genes [protein tyrosine phosphatase, non-receptor-type 11 (PTPN11), RAF, NF, HRas proto-oncogene, GTPase (HRAS), B-Raf proto-oncogene, serine/threonine kinase (BRAF), MEK1/2, KRAS proto-oncogene, GTPase (KRAS), SOS Ras/Rho guanine nucleotide exchange factor 2 (SOS2), leucine rich repeat scaffold protein (SHOC2), NRAS proto-oncogene, GTPase (NRAS), and Raf-1 proto-oncogene, serine/threonine kinase (RAF1)],

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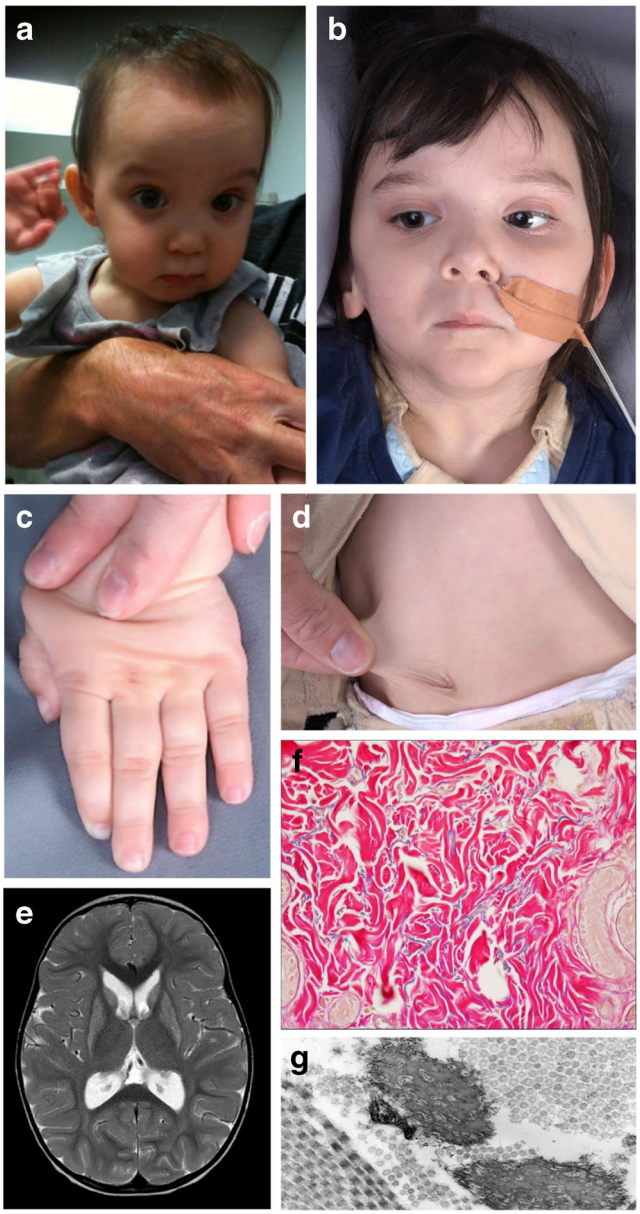

Fig. 1 **a** Soft dysmorphic features at 17 months of high forehead, bilateral epicanthic folds, flat nasal bridge, sparse scalp hair, long philtrum, and sagging cheeks. **b** Facial features at 4.5 years of age of high forehead, bilateral epicanthic folds, flat nasal bridge, and long philtrum. **c** Loose skin folds over hand at 4.5 years of age. **d** Loose, inelastic skin over abdomen at 4.5 years of age. **e** Bilateral symmetrical high T2 signals in globus pallidi, putamen, and head of caudate nuclei displayed on brain magnetic resonance imaging (MRI) done at 15 months of age. **f** Light microscopy of skin (Miller's stain) showing scarce, fragmented elastic fibers. **g** Electron microscopy of skin showing moth-eaten appearance of elastic bundles

which regulate the Ras-MAPK cascade. Here, we further expand the list of inborn errors of metabolism associated with cutis laxa by describing the clinical presentation of a 17-month-old girl with Leigh-like syndrome due to enoyl coenzyme A hydratase, short chain, 1, mitochondria (ECHS1) deficiency, a mitochondrial matrix enzyme that catalyzes the second step of the beta-oxidation spiral of fatty acids and plays an important role in amino acid catabolism, particularly valine.

Summary

A 17-month-old Caucasian girl presented with global developmental delay, postnatal failure to thrive, and central hypotonia. Clinical examination revealed soft dysmorphic features (high forehead, bilateral epicanthic folds, flat nasal bridge, sparse scalp hair, long philtrum, and sagging cheeks (Fig. 1a), choreoathetoid movements, truncal ataxia, brisk reflexes, joint hypermobility, and cutis laxa with loose, inelastic

skin (Fig. 1b–d images taken at 4.5 years of age). Formal ophthalmological assessment and newborn screening hearing test were normal.

Initial investigations showed persistent mild lacticacidemia (range 3.9–5.4 mmol/L; reference range 0.0–3.0), normal plasma amino acids, urine organic and amino acid analysis, creatine kinase, serum copper, ceruloplasmin, transferrin isoforms, apolipoprotein C-III (apo-CIII), and array comparative genomic hybridization (aCGH). Brain magnetic resonance imaging (MRI) displayed bilateral symmetrical high T2 signals in globus pallidi, putamen, and head of caudate nuclei (Fig. 1e). Light microscopy of skin biopsy showed classic cutis laxa features, with scarce, fragmented elastic fibers (Fig. 1f) and moth-eaten appearance of elastic bundles on electron microscopy (Fig. 1g). Skeletal muscle respiratory chain enzymology, mitochondrial DNA (mtDNA) common point mutation analysis, Sanger sequencing of *PYCR1* and *ALDH18A1*, and whole-exome sequencing results were noncontributory. Previously reported compound heterozygous variants p.Gln159Arg; p. Thr180Ala were identified in the *ECHS1* gene (Tetreault et al. 2015) through whole-genome sequencing and confirmed by Sanger sequencing. Parents were heterozygous for variants.

ECHS1 encodes enoyl-CoA hydratase, short chain 1, a multifunctional mitochondrial matrix enzyme crucial in valine metabolism and of limited importance in the oxidation of fatty acids. Prominent clinical features include encephalopathy, deafness, epilepsy, optic atrophy, cardiomyopathy, lacticacidemia, and neuroimaging consistent with Leigh-like syndrome. Affected individuals may show abnormal plasma acylcarnitines, increased urine 2-methyl, 2,3-dihydroxybutyrate, reduced tissue respiratory chain enzyme activity, and/or reduced fibroblast pyruvate dehydrogenase enzyme activity.

Interestingly, cutis laxa, a feature of several neurometabolic disorders, has never been described in *ECHS1* deficiency. Hence, it could potentially be considered as a differential of metabolic cutis laxa syndromes.

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Compliance with ethical standards

Conflict of interest S. Balasubramaniam, L. G. Riley, D. Bratkovic, D. Ketteridge, N. Manton, M. J. Cowley, V. Gayevskiy, T. Roscioli, M. Mohamed and T. Gardeitchik declare they have no conflict of interest. E. Morava is the Editor-in-Chief of the *Journal of Inherited Metabolic Disease*. J. Christodoulou is a communicating editor of the *Journal of Inherited Metabolic Disease*.

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