Lethal neonatal case and review of primary short-chain enoyl-CoA hydratase (SCEH) deficiency associated with secondary lymphocyte pyruvate dehydrogenase complex (PDC) deficiency.

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Abstract
Mutations in ECHS1 result in short-chain enoyl-CoA hydratase (SCEH) deficiency which mainly affects the catabolism of various amino acids, particularly valine. We describe a case compound heterozygous for ECHS1 mutations c.836T>C (novel) and c.8C>A identified by whole exome sequencing of proband and parents. SCEH deficiency was confirmed with very low SCEH activity in fibroblasts and nearly absent immunoreactivity of SCEH. The patient had a severe neonatal course with elevated blood and cerebrospinal fluid lactate and pyruvate concentrations, high plasma alanine and slightly low plasma cystine. 2-Methyl-2,3-dihydroxybutyric acid was markedly elevated as were metabolites of the three branched-chain α-ketoacids on urine organic acids analysis. These urine metabolites notably decreased when lactic acidosis decreased in blood. Lymphocyte pyruvate dehydrogenase complex (PDC) activity was deficient, but PDC and α-ketoglutarate dehydrogenase complex activities in cultured fibroblasts were normal. Oxidative phosphorylation analysis on intact digitonin-permeabilized fibroblasts was suggestive of slightly reduced PDC activity relative to control range in mitochondria. We reviewed 16 other cases with mutations in ECHS1 where PDC activity was also assayed in order to determine how common and generalized secondary PDC deficiency is associated with primary SCEH deficiency. For reasons that remain unexplained, we find that about half of cases with primary SCEH deficiency also exhibit secondary PDC deficiency. The patient died on day-of-life 39, prior to establishing his diagnosis, highlighting the importance of early and rapid neonatal diagnosis because of possible adverse effects of certain therapeutic interventions, such as administration of ketogenic diet, in this disorder. There is a need for better understanding of the pathogenic mechanisms and phenotypic variability in this relatively recently discovered disorder.

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