4. Biochemical, molecular, and clinical characteristics of children with short chain acyl-CoA dehydrogenase deficiency detected via newborn screen in the state of California

Natalie M. Gallant[1], Karen Leydiker[2], Hao Tang[3], Lisa Feuchtbaum[3], Fred Lorey[3], Naghmeh Dorrani[1], Erica Chang[1], Rebecca Puckett[2], Bruce A. Barshop[4], Stephen D. Cederbaum[1], Jose E. Abdenur[2], Raymond Y. Wang[2]

[1]*Departments of Pediatrics and Human Genetics, University of California at Los Angeles, Los Angeles, CA, USA*
[2]*Division of Metabolic Disorders, Pediatric Subspecialty Faculty, CHOC Children's, Orange, CA, USA*
[3]*Genetic Disease Branch, California Department of Health Services, Richmond, CA, USA*
[4]*Department of Pediatrics, Rady Children's Hospital-San Diego, University of California at San Diego, La Jolla, CA, USA*

Background: Short-chain acyl-CoA dehydrogenase deficiency (SCADD) is an autosomal recessive inborn error of mitochondrial fatty acid oxidation with highly variable biochemical, genetic, and clinical characteristics. SCADD has been associated with accumulation of butyryl-CoA byproducts, including butyrylcarnitine (C4), butyrylglycine, ethylmalonic acid (EMA), and methylsuccinic acid (MS) in body fluid and tissues. Differences in genotype frequencies have been shown between patients diagnosed clinically vs. those diagnosed via newborn screen (NBS). Moreover, while patients diagnosed clinically have a variable clinical presentation including developmental delay, ketotic hypoglycemia, epilepsy and behavioral disorders, studies suggest patients diagnosed via NBS are largely asymptomatic. Scant information is published about the biochemical, genetic and clinical outcome of SCADD patients diagnosed via NBS.

Methods: We collected California NBS, follow-up biochemical levels, and ACADS mutation data from September, 2005 through April, 2010. We retrospectively reviewed available data on SCADD cases diagnosed by NBS from three newborn screen referral centers for clinical outcomes.

Results: During the study period, 2,632,058 newborns were screened and 74 confirmed SCADD cases were identified. No correlations between initial (NBS) C4 value and follow-up biochemical markers (C4, EMA or MS levels) were found in the 74 cases studied. We found significant correlation between follow-up C4 vs. urine EMA ($R^2 = 0.51$, $p < 0.0001$) and follow-up C4 vs. urine MS ($R^2 = 0.45$, $p < 0.0001$). Of 21 cases where ACADS gene sequencing was performed: 6 had two or more disease-causing mutations; 7 were compound heterozygotes for a deleterious mutation and common polymorphism; 7 were homozygous for the common polymorphism c.625G>A; and 1 was heterozygous for c.625G>A. A statistically significant increase in mean EMA level was noted in patients with two or more deleterious mutations vs. mutation heterozygotes ($p = 0.02$) or common polymorphism homozygotes ($p = 0.005$). Clinical outcome data was available in 31 patients. None developed epilepsy or behavioral disorders, and only one patient had isolated speech delay. Over time, parents refused long-term follow-up in a significant number of cases (12/31). Hypoglycemia (blood glucose<60 mg/dL) occurred in two patients, both solely in the neonatal period: one with meconium aspiration and one instance of hypoglycemia; the other with central apnea, poor feeding, and hypotonia. The latter, a c.625G>A polymorphism homozygote, has had persistent elevations in both short- and medium-chain acylcarnitines; diagnostic workup is ongoing.

Conclusions: Our study examines the largest series to date of SCADD patients identified via NBS. Our results suggest that biochemical confirmatory tests may be useful to differentiate patients with common polymorphisms from those with disease-causing mutations. Even in those patients with disease-causing mutations, SCADD diagnosed via NBS appears to present largely as a benign condition.