Newborn Screening, Inborn Errors of Metabolism

AB076. Heterozygous carriers of succinyl-CoA:3-oxoacid CoA transferase deficiency can develop severe ketoacidosis

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Background: Succinyl-CoA:3-oxoacid CoA transferase (SCOT, gene symbol *OXCT1*) deficiency is an autosomal recessive disorder of ketone body utilization that results in severe recurrent ketoacidotic episodes in infancy. More than 30 patients with this disorder have been reported and to our knowledge, their heterozygous parents and siblings have had no apparent ketoacidotic episodes.

Methods: PCR-sequencing, multiplex ligation-dependent probe amplification analysis on the *OXCT1* gene was performed to identify mutations. Study of pathogenic mechanism of the mutants identified was performed.

Results: Over 5 years [2008–2012], we investigated several patients that presented with severe ketoacidosis and identified a heterozygous *OXCT1* mutation in four of these cases (Case1 p.R281C, Case2 p.T435N, Case3 p.W213*, Case4 c.493delG). To confirm their heterozygous state, we performed a multiplex ligation-dependent probe amplification analysis on the *OXCT1* gene which excluded the presence of large deletions or insertions in another allele. A sequencing analysis of subcloned full-length SCOT cDNA showed that wild-type cDNA clones were present at reasonable rates to mutant cDNA clones. Over the following 2 years [2013–2014], we analyzed *OXCT1* mutations in six more patients presenting with severe ketoacidosis (blood pH <7.25 and total ketone body >10 mmol/L) with non-specific urinary organic acid profiles. Of these, a heterozygous *OXCT1* mutation was found in two cases (Case5 p.G391D, Case6 p.R281C). Moreover, transient expression analysis revealed R281C and T435N mutants to be temperature-sensitive. This characteristic may be important because most patients developed ketoacidosis during infections.

Conclusions: Our data indicate that heterozygous carriers of *OXCT1* mutations can develop severe ketoacidotic episodes in conjunction with ketogenic stresses.

Keywords: Succinyl-CoA:3-oxoacid CoA transferase deficiency (SCOT); ketoacidosis; heterozygous carriers

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