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### SHORT/BRANCHED-CHAIN ACYL-CoA DEHYDROGENASE DEFICIENCY IN A TAIWANESE INFANT IDENTIFIED BY MS/MS NEWBORN SCREENING

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**Background**: Short/branched-chain acyl-CoA dehydrogenase (SBCAD) deficiency (OMIN No. 600301) is an inherited metabolic disorder of L-isoleucine catabolism. Mutation in the gene encoding short/branched-chain acyl-CoA dehydrogenase (*ACADSB*) leads to accumulation of 2-methylbutylglycine in urine and 2-methylbutyl (C5) carnitine in blood, by which SBCAD deficiency is also known as 2-methylbutyryl-CoA dehydrogenase (2MBCD) deficiency (OMIM No. 610006). Newborn screening by MS/MS technology in Taiwan is officially expanded for diseases with elevated C5 carnitine in July, 2006. In this study, an asymptomatic newborn with SBCAD deficiency was detected by the newborn screening program.
**Methods**: Samples from infant with elevated C5 carnitine were analyzed by GC/MS for urine organic acids. Mutations in the *ACADSB* gene were identified by PCR-based direct sequencing.
**Results**: This patient showed persistent elevation of C5 carnitine in 4 separate blood spot samples at age of 2, 8, 10 and 15 days. Organic acids analysis did not show accumulation in the urine at age of 16 days, however, an elevated 2-methylbutyrylglycine was detected in the urine at age of 32 days without clinical presentations. Molecular genetic analysis for this patient revealed a compound heterozygote of c.275C>G (p.Ser92X) and c.655G>A (p.Val219Met) in the *ACADSB* gene. These two novel variations were absent among 50 normal individuals and confirmed the SBCAD deficiency.
**Conclusions**: Asymptomatic SBCAD deficiency could be identified by MS/MS screening for newborns. Urine organic acids should be followed up in different life stages for newborns with elevated C5 carnitine to confirm diagnosis of SBCAD deficiency.

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### A NEW CASE OF SHORT/BRANCHED-CHAIN ACYL-CoA DEHYDROGENASE DEFICIENCY CAUSED BY TWO NOVEL MUTATIONS

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Short/branched-chain acyl-CoA dehydrogenase deficiency is an autosomal recessive defect in the S-pathway of isoleucine catabolism. Although few patients have been reported so far, they show a variety of clinical presentations. Some were diagnosed after metabolic/neurological presentation; others were diagnosed by neonatal screening and treated presymptomatically; others remain asymptomatic without any treatment. We report a new symptomatic case of SBCADD of Italian origin, identified by MS/MS newborn screening. Acylcarnitine and amino acid MS/MS analysis of patient's neonatal blood spot, showed an isolated increase of C5-acylcarnitine (0.96 μM; cut-off: 0.48 μM) and C5/C2, C5/C3 ratios. An elevation of 2-methylbutyrylglycine associated to an increase of 2-ethylhydracrylic acid in urine obtained by GC/MS organic acid analysis, suggested the diagnosis of SBCAD deficiency. *ACADSB* gene sequencing analysis showed a missense mutation in exon 6 P262L (c.785 C>T) and an insertion at the donor splice site in intron 9: (g.42159_42160insT). Both mutations were not found in 116 normal chromosome. RT-PCR of full length cDNA showed the presence of two transcripts. Their analysis by sequencing showed the skipping of exon 9 in the shorter fragment. The present patient was born from a triple pregnancy. A prenatal ultrasonography at 30 weeks of gestation revealed shunting of blood between two fetuses. The intrauterine death of the donor fetus occurred at 31 weeks of gestation and a caesarean section was performed for fetal distress. The clinical presentation in this patient was therefore complicated by cerebral prenatal damage and we think that this serious illness could overlap the adverse effect of SBCADD.

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### OXIDATIVE STRESS IS INDUCED IN SUCCINATE SEMIALDEHYDE DEHYDROGENASE NULL MICE

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The mechanisms involved in the pathophysiology of succinate semialdehyde dehydrogenase (SSADH) deficiency remain largely unresolved. Therefore, in the present study we evaluated antioxidant defenses and lipid peroxidation in various cerebral structures (cortex, cerebellum, thalamus and hippocampus) and in the liver of SSADH deficient mice. We first observed that the tissue non-enzymatic antioxidant defenses were significantly reduced in the SSADH deficient animals, particularly in the liver (decreased total radical-trapping antioxidant potential and GSH) and in the cerebral cortex (decreased GSH), as compared to the wild type mice. Furthermore, superoxide dismutase activity was increased in the liver and cerebellum, whereas the activity of catalase was higher in the thalamus. In contrast, glutathione peroxidase activity was diminished in the hippocampus. Finally, lipid peroxidation (thiobarbituric acid-reactive substances) was markedly increased in the liver and cerebral cortex, reflecting a high lipid oxidative damage in these tissues. Our data showing an imbalance between tissue antioxidant defenses and oxidative attack strongly indicate that oxidative stress is involved in the pathophysiology of SSADH deficiency in mice, and likely the corresponding human disorder.

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### $^{11}$C-FLUMAZENIL PET IMAGING IN PATIENTS WITH SSADH DEFICIENCY

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**Background**: Succinic semialdehyde dehydrogenase (SSADH) deficiency is an autosomal recessive disorder of gamma-aminobutyric acid (GABA) metabolism characterized by elevated levels of GABA and gamma-hydroxybutyric acid (GHB). Clinical findings include mental retardation with disproportionate expressive language dysfunction, hypotonia, hyporeflexia, hallucinations, autistic behaviors and seizures. Autoradiographic labeling and slice electrophysiology studies in the murine model provide evidence for use-dependent down-regulation of the GABA(a) receptor. We investigated benzodiazepine receptor (BZPR) binding in patients with SSADH deficiency using [$^{11}$C] flumazenil (FMZ) and positron emission tomography (PET).
**Methods**: FMZ binding was measured in 6 patients with SSADH deficiency,and 10 unaffected parents (obligate heterozygotes). We performed PET on a GE Advance Scanner using a reference region compartmental model, with time-activity curve from pons as the input function. Relative parametric binding potential (BP) was derived, with MRI-based pixel by pixel partial volume correction, in regions of interest drawn on co-registered MRI.
**Results**: In hippocampus, amygdala, thalamus, caudate, frontal cortex, occipital cortex, and cerebellar vermis, patients with SSADH deficiency had 25–45% significant reductions in FMZ BP compared to parents. There was no effect of gender.
**Conclusions**: SSADH deficient patients show widespread reduction in BZPR binding on $^{11}$C-FMZ PET. Since previous studies of FMZ PET have shown that binding is higher in children, our results suggest that high endogenous brain GABA levels in SSADH deficiency down-regulate GABA(a)-BZPR binding site availability.