Succinic Semialdehyde Dehydrogenase Deficiency in a Chinese Boy: A Novel ALDH5A1 Mutation With Severe Phenotype

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Abstract
Succinic semialdehyde dehydrogenase deficiency is a rare autosomal recessive disorder affecting catabolism of the neurotransmitter gamma-aminobutyric acid (GABA) with a wide range of clinical phenotype. We report a Malaysian Chinese boy with a severe early onset phenotype due to a previously unreported mutation. Urine organic acid chromatogram revealed elevated 4-hydroxybutyric acid. Magnetic resonance imaging (MRI) of the brain demonstrated cerebral atrophy with atypical parietal involvement. Molecular genetic analysis showed a novel homozygous 3-bp deletion at the ALDH5A1 gene c.1501_1503del (p.Glu501del). Both parents were confirmed to be heterozygotes for the p.Glu501del mutation. The clinical course was complicated by the development of subdural hemorrhage probably as a result of rocking the child to sleep for erratic sleep-wake cycles. This case illustrates the need to recognize that trivial or unintentional shaking of such children, especially in the presence of cerebral atrophy, can lead to subdural hemorrhage.

Keywords
sucinic semialdehyde dehydrogenase deficiency, subdural hemorrhage, ALDH5A1 gene

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Succinic semialdehyde dehydrogenase deficiency is a rare autosomal recessive disorder resulting in the failure of the degradation of succinyl semialdehyde leading to accumulation of 4-hydroxybutyric acid (GHB) in the body. Succinic semialdehyde dehydrogenase deficiency is typically a slowly progressive or static encephalopathy with late infantile to early childhood onset. The clinical phenotype is variable ranging from mild to severe neurologic deficits including psychomotor retardation, hypotonia, seizures, ataxia, abnormal sleep patterns, and behavioral problems. Diagnosis of succinic semialdehyde dehydrogenase deficiency is suggested by the excretion of GHB in the body fluids and confirmed by either succinic semialdehyde dehydrogenase enzyme activity or molecular genetic analysis of ALDH5A1 gene.

We report on a child with a novel mutation of the ALDH5A1 gene manifesting with a severe phenotype. This patient had atypical radiologic features and a clinical course that was complicated by the development of a subdural hemorrhage.

Case Report
A Chinese boy presented to our hospital with hypotonia and intractable seizures at 4 months of age. He was born at term with a birth weight of 3.1 kg and there were no significant perinatal events. The parents were first cousins, with significant consanguinity in previous generations, and had a healthy 2-year-old daughter. Multiple seizure types started within 1 month of age, including tonic spasms, hemifacial clonic or tonic seizures, and variable head and eye deviation. Treatment with multiple antiepileptic drugs (clonazepam, valproic, topiramate, phenytoin, phenobarbital, and midazolam) and pyridoxine were ineffective. Initial magnetic resonance imaging (MRI) of his brain at 3 months revealed mild cerebral atrophy with delayed myelination.

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