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 putaminal 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
succinic semialdehyde dehydrogenase deficiency, subdural hemorrhage, ALDH5A1 gene

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, hemifocal clonic or tonic seizures, and versive head and eye deviation. Treatment with multiple antiepileptic drugs (clonazepam, valproate, topiramate, phenytoin, phenobarbitone, 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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When referred to our hospital at age 4 months, he had multiple daily seizures. Physical examination revealed axial and truncal hypotonia, generalized hyporeflexia, and global developmental delay. The electroencephalography (EEG) showed markedly disorganized background activity and frequent high-voltage slow waves, sharp waves, and spikes maximal over the posterior quadrants (Figure 1). The urine organic acid chromatogram revealed a large peak of GHB which was suggestive of succinic semialdehyde dehydrogenase deficiency. Following written informed consent from the parents, molecular genetic analysis of the \textit{ALDH5A1} gene was performed on his peripheral blood leukocytes. Polymerase chain reaction amplification followed by conventional sequencing of all exons including splice sites was performed. Analysis and alignment were done using Bioedit Sequence Alignment Editor v7.1.3.0 and the \textit{ALDH5A1} reference sequence (accession number: NG008161.1), respectively. A homozygous GAG deletion at position c.1501_1503 was identified (Figure 2). In addition, 3 common homozygous missense variants (p.Gly36Arg, p.His180Tyr and p.Pro182Tyr) were also found. Biological impact from the c.1501_1503del mutation was predicted using the PROVEAN (v1.1.3) protein variation effect software. This deletion was predicted to be deleterious with a score of −5.598 (threshold value = −2.5). Both parents were confirmed to be heterozygotes for c.1501_1503del (Figure 2).

He was started on oral vigabatrin and levetiracetam, gradually increasing to 65 mg/kg/d. Seizure frequency was reduced from 10-15 attacks to 4-5 attacks daily, with occasionally no seizures noted in a day. All other medications were discontinued. A repeat EEG showed improvement of background activity (Figure 1). At 5 months of age, he developed erratic sleep-wake cycles, whereby he would remain awake for prolonged periods in the night with intermittent brief naps throughout the day, which was followed by inconsolable crying whenever he was awake. A trial of melatonin was not effective. The caregiver reported that he needed to be carried, patted, and rocked to sleep. Seizure activity remained unchanged throughout. He was readmitted for observation and respite care as the caregiver was physically exhausted from lack of sleep and the continuous need to carry and rock him. A repeat EEG did not reveal any increase in epileptiform discharges. Investigations for gastroesophageal reflux disease, hip subluxation, and occult infections were negative. Sedatives like chloral hydrate and benzodiazepines were only partially effective.

![Figure 1. Electroencephalography (EEG) showed frequent high-voltage sharp slow waves and spikes maximal over the posterior quadrants (left); improvement of background activity following therapy (right).](image1.png)

![Figure 2. Electropherogram for parent 1 (top), parent 2 (middle), and patient (bottom). Both parents are heterozygotes for c.1501_1503del. The electropherogram for the patient shows a homozygous GAG deletion (c.1501_1503del) at the ALDH5A1 gene.](image2.png)
levetiracetam dosages were reduced to determine if these could contribute to his “behavioral problems” but these measures did not improve his condition.

A subsequent MRI of the brain was performed when he was 8 months old, which incidentally revealed a left frontal-parietal subacute subdural bleed with marked cerebral atrophy. In addition, there were high T2-weighted signal abnormalities in the putamina and atrophy of the caudate nuclei bilaterally without atrophy or signal change in the cerebellum (Figure 3). The white matter myelination was appropriate for age and there were no other abnormal signal changes in the rest of the brain parenchyma.

No retinal hemorrhages were noted. The subdural bleed was managed conservatively as a follow-up computed tomography (CT) of the brain showed a decrease in its size. The family admitted to rocking to calm him during the crying episodes. The parents and caregivers were advised on the potential complications of shaking the infant vigorously and were educated on alternative responses to persistent infant crying.

At age 1 year 5 months, he presented with refractory status epilepticus following a febrile illness and required intravenous phenytoin as well as midazolam infusion and ventilatory support. Although his seizure semiology remained unchanged, the frequency increased up to 70 times per day. Clobazam was introduced (stepping up to 1.6 mg/kg/d) and vigabatrin was increased to 107 mg/kg/d. His seizures were reasonably controlled and levetiracetam was weaned off subsequently. He was discharged with clobazam and vigabatrin.

A follow-up clinical review at age 2 years revealed that the child remained bed-ridden, hypotonic, and severely delayed without gaining any new skills like visual fixation or head control. Periods of erratic sleep and intractable seizures waxed and waned. Vigabatrin was gradually reduced to 55 mg/kg/d without worsening of seizure activity.

Discussion

Succinic semialdehyde dehydrogenase deficiency was first reported in a child with neurologic abnormalities in 1981.\textsuperscript{2} Identification of the gene for succinic semialdehyde dehydrogenase (ALDH5A1) in chromosome 6p22 was reported in 1996 and later the complete open reading frame was found to consist of 1605 bp (accession number: Y11192) within 10 exons coding for 535 amino acids and the first 47 residues
recognized as putative mitochondrial targeting peptide. A wide spectrum of ALDH5A1 mutations had been reported from various geographic origins. However, to date, genotype-phenotype correlation is scanty and there is no constant relationship between the residual succinic semialdehyde dehydrogenase activities and the disease phenotype.

Here we describe a young boy with a homozygous deletion (c.1501_1503del) occurring concomitantly with 3 common homozygous missense variants (p.Gly36Arg, p.His180Tyr and p.Pro182Tyr) in ALDH5A1. The c.1501_1503del mutation has not been previously reported and was not found in a succinic semialdehyde dehydrogenase deficiency database containing approximately 13 000 control alleles maintained by the University of Washington, Seattle (http://evs.gs.washington.edu/EVS/). Notwithstanding the deleterious effect of p.Glu501del per se, the concomitant presence of the 3 other missense variants in our patient may have resulted in a further decrease of succinic semialdehyde dehydrogenase activity as reported by Akobashi et al.

The neuroimaging abnormalities of succinic semialdehyde dehydrogenase deficiency commonly demonstrate a pallidodentatoluysian pattern with T2 hyperintensities in the globus pallidi, cerebellar dentate nuclei, and subthalamic nuclei bilaterally and symmetrically. Subcortical white matter, thalamus and brainstem involvement, delayed myelination, and cerebral and cerebellar atrophy have been described as well. However, variations occur with occasionally asymmetric involvement or only partial involvement of these structures. Putamina and caudate nuclei abnormalities without cerebellar involvement have been recognized in a severe phenotype of succinic semialdehyde dehydrogenase deficiency by Yamakawa et al. Our patient had strikingly similar radiologic features, and detailed review of future patients may help clear the ambiguity as to whether these patterns of MRI abnormalities actually represent a more severe phenotype.

The incidental finding of subacute subdural hemorrhage in our patient highlights an increased vulnerability of subdural hemorrhage in children with neurometabolic disorders.

Some rare metabolic diseases, particularly glutaric aciduria, present with progressive cerebral atrophy associated with subdural hemorrhages, occurring either spontaneously or following trivial head injury. Other rare neurometabolic disorders that manifest similarly include Menkes disease, D-2 hydroxyglutaric aciduria, methylmalonic aciduria, and homocystinuria (cblC). Some of these cases have been initially misinterpreted as non-accidental injury. Thus, accurate diagnosis has important social and potential therapeutic implications. The formation of such a subdural hemorrhage is postulated to be due to the shearing of cortical veins that become more vulnerable as cerebral atrophy progresses and the brain recedes from the dura. Abnormal cerebral vasculature or direct vascular endothelial damage from accumulation of toxic metabolites are plausible underlying causes. These changes potentially increase the fragility of the vessels and lead to bleeding with minimal or no trauma. However, we believe that, in addition to the underlying cerebral atrophy, rocking was a possible confounding factor in the precipitation of the subdural hemorrhage in our patient.

Behavioral problems and sleep disturbances are not uncommon in succinic semialdehyde dehydrogenase deficiency. It should be recognized that persistent crying can be a major stressor for exhausted or frustrated caregivers of children with neurodevelopmental disability, and they should receive anticipatory guidance on the consequences of infant shaking especially if cerebral atrophy is a complication of the primary disease.

Conclusion
Identification of a novel mutation in our patient with a severe early-onset phenotype of succinic semialdehyde dehydrogenase deficiency is an important addition to the catalog of disease-causing ALDH5A1 mutations. We believe this is the first reported case of succinic semialdehyde dehydrogenase deficiency with subdural hemorrhage. Although the subdural hemorrhage can be attributed to the progressive cerebral atrophy, caregivers of these children are often unaware of this potential complication. Education and dissemination of information about the consequences of infant rocking or shaking should be part of the counselling process.

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Author Contributions
CGT was involved in the care of the patient and prepared the first draft. LCO and SY revised the article and also were actively involved in the management of the patient. PS was responsible for metabolic laboratory support. HA provided genetic laboratory support and genetic inputs. KR provided radiologic inputs. All authors approved the final version of the article.

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Ethical Approval
Written consent was obtained from the parents for publication of the case report.

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