Infantile Spasms and Hyperekplexia Associated With Isolated Sulfite Oxidase Deficiency

J. Lloyd Holder Jr, MD, PhD; Satish Agadi, MD; William Reese, BA; Catherine Rehder, PhD; Michael M. Quach, MD

Important: Isolated sulfite oxidase deficiency (ISOD) causes severe intellectual disability, epilepsy, and shortened life expectancy. Intractable seizures are invariable in children with ISOD; however, to our knowledge, infantile spasms with a corresponding hypsarrhythmia pattern on electroencephalogram have never been reported. In addition, the nonepileptic paroxysmal movement disorder hyperekplexia has never previously been reported with ISOD.

Observations: We describe an infant with ISOD who initially presented with neonatal seizures, diffusion restriction noted on magnetic resonance imaging, and elevated serum S-sulfocysteine consistent with ISOD. A homozygous mutation in the SUOX gene was identified, confirming the diagnosis. Uniquely, this patient developed a profound accentuated startle response that did not have a corresponding electrographic change on electroencephalogram consistent with hyperekplexia. This was followed by a change in the child’s electroencephalogram to the chaotic pattern of hypsarrhythmia and brief tonic seizures with attenuation of the hypsarrhythmia pattern characteristic of infantile spasms.

Conclusions and Relevance: The evolution of seizures associated with ISOD is poorly characterized because of the small number of patients. We report what we believe to be the first case of a child with ISOD who developed infantile spasms and hyperekplexia. This expands the phenotypes associated with ISOD and also should caution clinicians to not assume that all abnormal movements are seizures.

Author Affiliations: Division of Neurology and Developmental Neuroscience, Department of Pediatrics, Baylor College of Medicine, Texas Children’s Hospital, Houston (Holder, Agadi, Quach); Clinical Molecular Diagnostic Laboratory, Duke University Health System, Durham, North Carolina (Reese, Rehder).

Corresponding Author: J. Lloyd Holder Jr, MD, PhD, Division of Neurology and Developmental Neuroscience, Department of Pediatrics, Baylor College of Medicine, Texas Children’s Hospital, 6701 Fannin St, Clinical Care Center, Ste 1250, Houston, TX 77030 (holder@bcm.edu).

Report of a Case

Our patient is a 36-week gestation boy born to a 40-year-old gravida 6, para 3 woman. The Apgar scores were 9 at 1 minute and 9 at 5 minutes. On the first day of life, he was noted to have episodes of myoclonic jerks and tonic extension of all extremities. On initial examination his weight was 3450 g (90th percentile); length, 48 cm (50th-75th percentile); and head circumference, 34.4 cm (90th percentile). Further examination revealed marked diffuse hypotonia but was otherwise unremarkable. An ophthalmologic examination revealed microspherophakia. His family history was significant for parental consanguinity, with the mother and father being second cousins. He had a brother who also developed neonatal seizures with a subsequent diagnosis of ISOD. The patient’s brother required a gastrostomy and tracheostomy and died at age 4 years from aspiration pneumonia.

The patient’s initial electroencephalogram (EEG) demonstrated a low-amplitude background with multifocal electrographic seizures of multiple abnormalities. On the fifth day of life, magnetic resonance imaging revealed widespread decreased diffusivity in the posterior frontal, parietal, and occipital lobes bilaterally, but no other structural abnormalities (Figure 1A). Magnetic resonance spectroscopy indicated abnormal elevation of lactate peaks in the bilateral basal ganglia, thalamus, and occipital lobes (Figure 1B). Serum S-sulfocysteine levels were elevated at 920 mmol per gram of creatinine. Xanthine and hypoxanthine levels were not el-
Sequencing of the SUOX gene (GenBank NT_029419.11) revealed a homozygous sequence change (Figure 2) at cDNA nucleotide 965 (exon 2). This change alters the lysine codon at position 322 to an arginine codon (p.Lys322Arg). This mutation has previously been reported and is postulated to be pathogenic owing to its position within the molybdenum cofactor-binding domain in close proximity to the enzyme-active site.

Administration of multiple antiepileptic medications resulted in only slight improvement in seizure frequency. Computed tomography of the head performed when the infant was 5 months revealed progressive degeneration of the brain with volume loss, cavitary lesions in the cerebral white matter, and bithalamic micromineralization (Figure 1C). By age 6 months, the infant’s head circumference was just 39 cm (less than the third percentile), and he continued to have generalized hypotonia with hyperreflexia and no motor or speech development. Further EEGs demonstrated continued multifocal sharp waves, but also episodes of 1 to 2 seconds of stiffening of his extremities with tactile stimulation not associated with an electrographic correlate; these episodes were
determined to be hyperekplexia. The episodes occurred more than 50 times per day and were reduced in frequency with the initiation of clonazepam at 0.01 mg/kg/d. Initiation of a formula with reduced sulfur-containing amino acids produced some improvement in seizure frequency, but hyperekplexia continued. When the patient was aged 15 months, his EEG showed changes to an extremely high voltage and chaotic background consistent with a hypersarrhythmia (Figure 1D). He also had several very brief tonic seizures preceded by attenuation of hypersarrhythmia, as well as continued episodes of hyperekplexia.

Discussion

Sulfite oxidase is the enzyme that catalyzes the final step in the metabolism of the sulfur-containing amino acids cysteine and methionine, converting sulfites to sulfates. Isolated sulfite oxidase deficiency has been reported to be associated with intractable neonatal seizures, acquired microcephaly, developmental delay, and early death. The accumulation of toxic sulfites results in the neurologic abnormalities and early death.

We describe a child with ISOD who developed hyperekplexia and, by age 15 months, infantile spasms. Children with ISOD invariably develop intractable neonatal seizures; however, all abnormal movements are not necessarily seizures. Our patient's startle episodes occurred more than 50 times per day and were mixed with electrographic seizures. Isolated sulfite oxidase deficiency results in progressive brain degeneration with cystic white matter lesions. Abnormal brain development is a common mechanism leading to infantile spasms; however, hypersarrhythmia and infantile spasms have not previously been reported in children with ISOD or deficiency of the molybdenum cofactor. This may be due, at least in part, to the early mortality seen in children with ISOD. Caution should be taken in assuming that all abnormal movements in children with ISOD or molybdenum cofactor deficiency are seizures.

ARTICLE INFORMATION

Accepted for Publication: September 6, 2013.

Author Contributions: Dr Holder had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Holder, Agadi.
Acquisition, analysis, or interpretation of data: Holder, Reese, Rehder, Quach.
Drafting of the manuscript: Holder, Agadi.
Critical revision of the manuscript for important intellectual content: Holder, Reese, Rehder, Quach.
Administrative, technical, or material support: Holder, Reese, Rehder, Quach.

REFERENCES