Infantile Spasms and Hyperekplexia Associated With Isolated Sulfite Oxidase Deficiency

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IMPORTANCE 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 not 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.

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isolated sulfite oxidase deficiency (ISOD) is a rare autosomal recessive disease with intractable neonatal seizures, severe developmental delay, neuroimaging mimicking hypoxic-ischemic encephalopathy, and early death.\(^1\) Sulfite oxidase binds a molybdenum-containing cofactor required for enzymatic activity. The molybdenum cofactor also complexes with xanthine dehydrogenase and aldehyde oxidase for their enzymatic activity. Deficiency of the molybdenum cofactor mimics the neurologic symptoms of ISOD. Although intractable epilepsy is a feature of ISOD, infantile spasms and hypsarrhythmia have not been reported. Exaggerated startle response or hyperekplexia has been reported\(^2\) in one child with deficiency of the molybdenum cofactor, but not in ISOD. We report on a child with confirmed ISOD, including intractable epilepsy and hyperekplexia, who developed hypsarrhythmia and infantile spasms.

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, thalami, 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-
Elevated lactate peak at 1.3 ppm. The peak values (left to right) are myo-inositol (mI), creatinine (Cr), glucose (Glx), mI, choline (Cho), Cr, N-acetylaspartic acid (NAA), Glx, and NAA. AU indicates arbitrary units. C, Sagittal section of a noncontrast computed tomography image of the head when the infant was aged 5 months. The arrowhead indicates the area of micromineralization. D, Electroencephalogram at 15 months with hypsarrhythmia background. EKG indicates electrocardiogram (red line); LOC-ROC, left-right ocular canthus (as a measure of muscle movement) (blue line).

Figure 2. Electropherogram of the SUOX Gene Mutation

Reference sequence: C T A A T C G G C
Patient sequence: C T A A T C C G G C

Homozygous mutation of the SUOX gene in exon 2 resulting in the substitution of arginine for lysine at position 322 (c.965 A>G; p. Lys322Arg), indicated with the arrow. The reference sequence used was GenBank Accession number NT_029419.11.
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 hypsarrhythmia (Figure 1D). He also had several very brief tonic seizures preceded by attenuation of hypsarrhythmia, 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, hypsarrhythmia 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

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REFERENCES