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Case 1: A term infant with apnea and stiffening

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PRESENTATION

A term male infant born via spontaneous vaginal delivery with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively, has an episode of apnea with stiffening and nonsuppressible whole body jerking for 2 minutes, occurring 5 hours after birth. Around 8 hours after birth, he has another episode but with exaggerated startle reflex, lip smacking, and eyelid fluttering. General examination shows no dysmorphic features, and findings are otherwise normal. Initial neurologic examination findings are unremarkable. Continuous electroencephalographic (EEG) monitoring with full neonatal montage is significant for intermittent sharp waves. Over the next day, the infant has 3 episodes of apnea with stiffening and nonsuppressible whole body jerking after each episode. These events are captured but EEG does not show them to be seizures. Initial management with phenobarbital and levetiracetam does not ameliorate spells.

His antenatal course is unremarkable. Family history is remarkable for consanguineous parentage of Middle Eastern descent (parents are first cousins of first cousins). Laboratory evaluation including serum and cerebrospinal fluid studies for infectious and metabolic etiologies shows normal findings. Magnetic resonance imaging (MRI) on day 5 after birth reveals normal brain structure with nonspecific hyperintense basal ganglia signal and minimal subdural hemorrhage from the birthing process. Five days later, findings of a repeat MRI with added spectroscopy are normal.

DISCUSSION

Diagnosis and Further Progress

Given the clinical suspicion for hyperekplexia, the patient was started on a trial of carbamazepine (15 mg/kg per day) and clonazepam (0.05 mg/kg per day) while continuing phenobarbital; with this regimen, he was spell-free for over a week before recurrence. Spells were eventually well controlled with a combination of clobazam (1.3 mg/kg per day) and clonazepam (0.15 mg/kg per day). Spells were acutely managed with the Vigevano maneuver (forcibly flexing legs to the trunk). When the spell did not respond to the maneuver, lorazepam was administered. Serial neurologic examinations revealed increased

tone and nonhabituating glabellar reflex with head retraction and spasms elicited by tapping the tip of the nose.

Single nucleotide polymorphism (SNP)-based microarray revealed no pathogenic deletions or duplications. Consistent with first-cousin consanguinity, copy neutral regions of homozygosity were detected, comprising 9.04% of the genome and containing approximately 127 gene candidates for unmasked recessive disorders. One of these was SLC6A5, located in a 28.3-Mb region of homozygosity (ROH) on chromosome 11p15.1, associated with autosomal recessive hyperekplexia type 3. Next-generation sequencing revealed a novel homozygous truncating SLC6A5 mutation (c.2077delCinsAAC; p.Leu693Asnfs*12) (NM_004211.3), consistent with disease-causing alleles.

The patient was discharged on nasogastric feeds and progressed to taking all feeds by mouth by 5 months of age. He was evaluated at 13 months of age and still found to have occasional stiffening spells but no myoclonic jerks. His motor development continues to be mildly delayed, with truncal hypotonia and weakness; he is now cruising and taking some steps independently. His spells are controlled with clobazam.

Typical Presentation in Newborns

Hereditary hyperekplexia is a rare movement disorder that manifests shortly after birth. Infants typically have generalized hypertonia while awake, which subsides when asleep. They also develop tonic spasms of the extremities and clenched fists that mimic tonic-clonic seizures. These episodes may lead to apnea and sudden infant death. They often have feeding difficulties and are at risk for aspiration. A pathognomonic feature is nonhabituation of startle elicited by tapping of the glabella or the philtrum¹.

Symptoms typically improve during the first few years after birth, with apnea episodes resolving by 2 years of age and hypertonia normalizing by 3 years of age. Developmental delays occur in approximately half of patients, with fewer having global intellectual disability. Patients may have a wide-based toddling gait that worsens when rushed and lingers until adolescence². The exaggerated startle, however, may persist lifelong and continue to pose a risk of uncontrolled falls².

Management

Clonazepam is the most efficacious treatment reported in cases of neonatal hyperekplexia¹. In the current case, clonazepam monotherapy was not sufficient to control startle symptoms. Clobazam as monotherapy has been published in the literature recently with good success in two severe infantile cases³. Clobazam was added to clonazepam with good results in our patient, and this combination was also found to be successful in a 7-year-old boy who had significant falls because of exaggerated startle⁴.

SLC6A5 (previously known as GLYT2; MIM 604159) encodes a 797-amino acid presynaptic glycine transporter localized to neurons of the medulla, spinal cord, and cerebellum.⁵ SLC6A5 mutations were discovered in patients with recessively inherited infantile hyperekplexia, including increased startle, muscular rigidity, and apnea. Mutations in postsynaptic glycine receptor genes GLRA1 and GLRB are associated with hyperekplexia

types 1 and 2, respectively.⁶ Genotype-phenotype correlation studies have demonstrated differences between the 3 types of known genetic hyperekplexia. Compared with those with GLRA1-associated hyperekplexia, patients with SLC6A5 mutations more frequently exhibit apnea (80% for SLC6A5 vs 43% for GLRA1) as well as developmental delays (74% vs 39%) and epilepsy (14% vs 5%).⁶ Long-term outcome in patients with SLC6A5-type hyperekplexia has not been well characterized. Given his age, we are not able to predict the severity of this condition in the current patient, and insufficient cases have been reported to determine whether nonsense mutations confer different disease severity from missense mutations for SLC6A5.⁶

A unique aspect of this case is identification of hyperekplexia secondary to mutations in SLC6A5 as the most likely diagnosis, based on ROH on microarray (Fig.). Genomic-based technologies such as SNP microarray allow for detection of copy-neutral ROH in addition to genomic deletions and duplications, not only to determine the extent of interrelatedness, but also to provide a list of candidate genes for unmasked recessive conditions⁷. Quickly obtaining the homozygous intervals increased the certainty of the clinical diagnosis, allowing us to conduct a trial of benzodiazepines before results of the *SLC6A5* gene sequencing were available. This improved control of his symptoms and permitted us to limit further medical and genetic evaluation.

Lessons for the clinician

- Hyperekplexia may present early in the neonatal period with seizure-like episodes.
- Clonazepam and clobazam combination therapy may control symptoms.
- Single nucleotide polymorphism microarray elucidates regions of homozygosity that may contain unmasked recessive disease genes with established parental consanguinity.

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Figure 1. Region of Homozygosity

SNP microarray detected a 15.1 Mb ROH on chromosome 11 (hg19,chr11:7619262-20019858), containing the *SLC6A5* gene (chr11:20,620,946-20,676,610) on chromosome 11p15.1.