A Case Study of a Child With Mitochondrial Disease

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KEYWORDS

Medication adverse reaction, mitochondrial disease, multisystem involvement, seizures

CASE PRESENTATION

A 4-year-old girl recently diagnosed with epilepsy presented to her pediatric advanced practice registered nurse (APRN) in a primary care clinic with 2 weeks of increased seizure activity after a medication change from carbamazepine to valproic acid. Symptoms also included a sudden increase in lethargy, ataxia, and drowsiness. She is co-managed by a pediatric neurologist for seizure control who was currently away from the office. Associated test results included a normal valproic acid level, elevated ammonia and liver function (Table 1), and an abnormal electroencephalogram reading; indicating a generalized process with ongoing focal-like features.

Seizure History

Two months prior, seizures began with the sudden onset of tonic–clonic events, requiring a 3-day hospitalization with observation for recurrent seizures or associated infection. After a second seizure, Phenytoin therapy was initiated, and she had no further seizures during the hospital stay. The child had no recent injuries, trauma, or known infections. Further metabolic studies were conducted to explore other possible causes with results pending. Magnetic resonance imaging was done and ruled out a tumor.

Two weeks after discharge, the child's seizures returned with daily occurrences of atypical absence (eye-blinking, head nodding, and staring) and tonic–clonic events. The child was referred to a pediatric neurologist and began taking carbamazepine. There was no additional seizure activity as the medication was increased to therapeutic levels. However, after 4 weeks of taking carbamazepine, seizure activity recommenced with at least one tonic–clonic seizure per day and multiple absence seizures that were "too many to count," at which time the child's medication was changed to valproic acid.

Past Medical History

The child was a singleton, born full term via caesarean birth because of placenta previa. She had mild hyperbilirubinemia with disproportionate flaccidity postnatally that resolved at home with sun exposure. She met all infant, toddler, and preschool developmental milestones including gross and fine motor, language, and psychomotor development. All recommended immunizations were up to date.

Family History

The child is the youngest of three children. There is no immediate family history of seizure activity. She has a first cousin with juvenile-onset myoclonic seizures controlled with medication. Her mother has a history of migraines, hearing loss, and hypothyroidism. Her father is in good health. No tobacco, recreational drugs, or alcohol are used in the household.

Review of Systems

Constitutional symptoms included increased drowsiness, slowing of speech, and difficulty staying awake throughout the day with general malaise and the need for frequent rest

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TABLE 1. Summary of pertinent laboratory values

Test	Value	Reference Range
Valproic acid (trough level)	58	55–100 μg/ml
Sodium	147	135–147 meq/L
Potassium	4.8	3.5–5.0 meq/L
Aspartate aminotransferase	**170**	<35 IU/L
Alanine aminotransferase	**360**	10–35 IU/L
Ammonia	**150**	15–45 μg/dl
Lactic acid, venous	**18.3**	8.1–15.2 mg/dl
Total bilirubin	**1.2**	0.3–1.0 mg/dl
Glucose	108	65–110 mg/dl
Hemoglobin	14	12–16 g/dl
Thyroid stimulating hormone	2	0.5–4.0 mU/L

Abnormal values are given in boldface.

periods, but no night sweats. In gastrointestinal review, the child was nauseated and had taken only sips of liquids. The child had a history of episodic abdominal pain and constipation. Musculoskeletal symptoms included that the child was fatigued and "wobbly" when walking from car to house according to her father. He stated that the child's activity improved with rest, requiring several hours to return to normal, and that the child's "muscles seem to be shrinking."

Physical Examination

The child, held in her mother's arms, was listless and difficult to arouse but was responsive to commands. She appeared fatigued and tearful, and she refused to ambulate. She was drowsy with slowed speech but responded to questions and was easily irritated. Her height and weight were in the 15th percentile, and her body mass index was in the 10th percentile for children of her age and sex. She was afebrile, with age-appropriate vital signs. Mild diffuse abdominal guarding was present during the examination, with tenderness over the right upper quadrant localized to the hepatic area; her abdomen was nondistended. Her musculoskeletal examination showed decreased muscle tone, mild muscle wasting, and decreased strength bilaterally. Her neurologic examination showed cranial nerves to be intact with slowed peripheral reflexes: 1+ lower extremities, 2+ upper extremities. There was no paresthesia or lack of sensation. There were multiple episodes of head nodding, eye rolling, and repetitive blinking during the examination.

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Differential Diagnoses

Using VINDICATE, a mnemonic to generate a thorough, organized, and systematic differential, the following systems-based etiologies were assessed: vascular, infectious, neoplastic, degenerative, iatrogenic/intoxication, congenital, autoimmune, traumatic, and endocrine/metabolic (Spinner, 2013). Most relevant differentials in this case included infection, neoplastic, degenerative, iatrogenic, congenital, and endocrine etiologies. Infection was ruled out because there were no recent episodes of active infection and the child was afebrile with a normal white blood cell count and differential. Neoplastic and congenital diagnoses were ruled out because of a recent negative result from head magnetic resonance imaging for neoplasm or tumor, with no abnormalities identified. The child was diagnosed with generalized epilepsy. However, recent attempts to control seizures with medication were unsuccessful. In fact, seizures worsened despite recent medication changes. Also, her ongoing lethargy, ataxia, and somnolence were inconsistent with typical generalized epilepsy; a degenerative diagnosis was considered because of her low body weight and motor deterioration with a decreased ability to ambulate and keep up with peers.

Iatrogenic/intoxication and endocrine/metabolic differentials were most likely. Although carbamazepine was used to initially control seizure activity, her seizures did not improve. Carbamazepine has been reported to have an uncommon adverse effect of exacerbating seizures in children with primary generalized epilepsy (Gansaeuer & Alsaadi, 2002). However, there was a recent medication change to valproic acid without improved seizure control. Associated abnormal laboratory test values included an elevated liver panel and elevated ammonia and lactic acid levels, suggesting metabolic and/or iatrogenic etiologies. The most likely differential resided in the following systems: degenerative, iatrogenic, and metabolic, and mitochondrial disease was diagnosed for this child.

DISCUSSION

Mitochondrial Disease

Mitochondrial disease is a common inborn error of metabolism, with a prevalence of 1:5,000, and occurs when there is a problem with cellular metabolism in the mitochondria (Parikh et al., 2015). Primary mitochondrial diseases arise from genetic mutations in nuclear DNA or mitochondrial DNA. They typically progress and affect multiple organ systems, especially those with high energy demands; the nervous system is highly vulnerable (Lawrence, Tompkins, & Taylor, 2014). The individual variation of symptoms and organs involved make this disease difficult to diagnose (Parikh et al., 2015). Mitochondria are responsible for the energy (adenosine triphosphate [ATP]) needed by the body to support organ function. When mitochondria are dysfunctional, cellular energy is insufficient, resulting in an inability of the mitochondria to produce enough energy for cell and organ function, ultimately causing cell injury or death. When this process occurs throughout the entire body, the patient experiences organ system failure (MitoACTION, 2017; United Mitochondrial Disease Foundation, 2017).

The diagnosis and treatment of mitochondrial disease is challenging and multifaceted. The Mitochondrial Medicine