A Young Child with Seizures and Mild Developmental Delay

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An 15-month-old previously healthy boy arrived at our emergency department (ED) via ambulance after a generalized seizure. The parents reported subjective fever, one episode of emesis, and nasal congestion a few hours prior to the convulsive spell.

Review of systems was negative for irritability or rash. Seizure was preceded by a transient unresponsive-ness followed by eye blinking, mouth twitching, and generalized tonic stiffness. Paramedics reported rectal temperature of 102.5°F and persistent seizure activity on their initial assessment. The patient received 0.2 mg of intranasal midazolam and had a rapid clinical response. The seizure lasted less than 10 minutes and was followed by post-ictal drowsiness and sleep. The child returned to normal mental status within the next 2 hours.

The child’s medical history was remarkable for borderline delay in developmental milestones, manifested by inability to walk independently and a limited vocabulary of only 4 words. There was no history of epilepsy in the family.

Initial physical assessment showed a well-nourished child with vital signs revealing rectal temperature up to 101.5°F. The head circumference showed relative microcephaly with head circumference between 80th and 90th percentile. There were no signs of trauma. Head, eyes, ear, nose, and throat (HEENT) examination was normal except for mucoid rhinorrhea. Cardiovascular and pulmonary examinations were unremarkable. Abdomen examination did not show hepatosplenomegaly or masses. There were no rashes or peripheral edema. Initial neurologic evaluation revealed an irritable young child without neck stiffness or focal motor deficit. He was able to crawl and stand on his own (no instability). There was no dysmetria or nystagmus.

While under observation in the ED, he had a second generalized tonic convulsive seizure that lasted for 30 seconds followed by post-ictal drowsiness. This prompted the medical staff to obtain neuroimaging. Subsequent computerized tomography (CT) imaging of the head demonstrated an abnormal low density throughout the frontal white matter and basal ganglia. Additional ED diagnostic workup included evaluation of cerebrospinal fluid indexes and complete liver and renal chemistries (which were normal). An electroencephalogram demonstrated bifrontal intermittent rhythmic delta activity.

For diagnosis, see page 236

Editor’s note: Each month, this department features a discussion of an unusual diagnosis in genetics, radiology, or dermatology. A description and images are presented, followed by the diagnosis and an explanation of how the diagnosis was determined. As always, your comments are welcome via email at Pediatrics@Healio.com.
Diagnosis:
Alexander Disease

The patient was admitted to our hospital for further management. A brain magnetic resonance imaging (MRI) scan was obtained that demonstrated symmetric area of increased T2 signals involving the supratentorial white matter (predominately anterior distribution) and central gray nuclei suggestive of Alexander disease (see Figure).

He was discharged on levetiracetam because of a high risk for recurrent seizures.

DISCUSSION
Alexander disease (AxD) is a rare neurodegenerative disorder characterized by progressive failure of central myelination.

Mutations in the glial fibrillary acidic protein (GFAP) gene lead to abnormal protein aggregation, which is thought to be the main cytotoxic mechanism in AxD.\(^1,2\) Abnormal polymerization of GFAP causes cytoskeleton instability as well.\(^3\)

GFAP mutations that affect the pediatric population are de novo. All of these are heterozygous (ie, only one allele) and act in a dominant fashion.\(^4\)

In our case, genetic testing reported abnormal DNA sequence variant in the GFAP gene, supporting a diagnosis of AxD. Inheritance in the adult-onset familial variant is autosomal dominant.\(^5\) A total of 72 distinct mutations have been identified to date.\(^6\)

Currently, there is no genetically engineered animal model that mimics all features of AxD in humans.

Typical histopathological findings reveal the presence of cytoplasmic inclusions within the astrocytes, termed “Rosenthal fibers.”\(^7\) These filament-like protein aggregates are composed mainly of GFAP and heat shock proteins.\(^8,9\) Widespread distribution of Rosenthal fibers is unique to AxD, but the focal pattern is present in other neurological conditions such as astrocytomas and multiple sclerosis.\(^2\)

AxD is very rare, but the actual incidence and prevalence rates are unknown; only 189 cases of AxD with GFAP mutations have been reported in the literature.\(^6\)
This leukodystrophic disorder usually has its onset in infancy or early childhood and is associated with macrocephaly, psychomotor retardation, seizures, and death in the first decade of life. Late-onset forms of AxD show a wide clinical variability.

A recently revised clinical classification of AxD proposed two distinct patterns of phenotypic expression (Type I and II) based on analysis of statistically defined patient groups. Type I AxD is characterized by early onset, seizures, macrocephaly, paroxysmal deterioration, failure to thrive, developmental delay, and typical neuroimaging features. Type II AxD occurs across the lifespan and is distinguished by autonomic dysfunction, bulbar symptoms, eye movement abnormalities, and atypical neuroimaging elements.

After a comprehensive analysis, van der Knaap et al proposed a set of neuroimaging diagnostic criteria for AxD. The presence of any 4 of the 5 criteria establishes an MRI-based diagnosis of AxD (see Sidebar, page 236). Larger case series with genetic assessments are needed to further clarify genotype-phenotype correlations.

AxD diagnosis is established based on clinical and radiological (MRI) criteria. GFAP gene analysis is not necessary but can be used to confirm the presumptive diagnosis. In one case report, elevated GFAP levels in cerebrospinal fluid were detected in three genetically confirmed cases of AxD.

Currently, only supportive treatment is available for AxD. The goal of treatment is to prevent, control, or relieve complications and to improve the patient’s quality of life. Genomic therapy seems to be a promising therapeutic intervention in the disease. Prenatal genetic counseling for families with increased risk may become possible if the disease-causing mutation is identified.

This case illustrates that diagnostic MRI abnormalities of AxD may be present at a very young age, long before the appearance of characteristic clinical signs. Early diagnosis allows prompt counseling of families.

REFERENCES