RESIDENT & FELLOW SECTION

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Clinical Reasoning: Novel GLUT1-DS mutation

Refractory seizures and ataxia

Sonali Sen, MD
Karen Keough, MD
James Gibson, MD, PhD

Correspondence to Dr. Sen: stsen@seton.org

ABSTRACT

Intractable epilepsy is a common diagnosis among child neurology practitioners with medical management remaining unsatisfactory in many cases. GLUT1 deficiency syndrome (GLUT1-DS) is a disorder that should be considered in such situations. Evaluation by comparing serum to CSF glucose levels is a fast and relatively easy test, with hypoglycorrhachia being highly suggestive of GLUT1-DS. Furthermore, treatment with the ketogenic diet is well-established and can result in significant improvement in quality of life for these patients. The following case report outlines the presentation of one such patient and highlights common features that can be seen with GLUT1-DS. Of interest, she was found to have a spontaneous, novel mutation that has not been reported previously. Her case allows us to expand on the present literature and demonstrate the improvements that can be seen in a child with appropriate treatment. *Neurology®* 2015;84:e111–e114

SECTION 1

An 18-month-old girl with intermittent paroxysmal events was brought to our clinic for workup. Medical history revealed recurrent 1- to 2-minute episodes of unresponsiveness, head rolling, and disconjugate gaze beginning around 3 months of age. Distinct from these events, she also had occasional dystonic posturing of her left arm. Prior MRI and 2 4-hour video EEGs were normal; medication had not been started due to the uncertain etiology of her episodes.

Brief unresponsive episodes were present in the setting of mild developmental delay; she sat at 7 months, walked at 16 months, and had 1 word and followed 2-step commands at 18 months. She had low muscle tone and poor coordination but her motor examination was symmetric.

Questions for consideration:

1. What should be included in the differential diagnosis?
2. Is further workup necessary at this time?

The differential diagnosis of paroxysmal neurologic events in infancy includes benign paroxysmal torticollis of infancy, benign paroxysmal vertigo, syncope, dyskinesias, migraines, Sandifer syndrome, and seizures. Persistent reports of stereotyped events, particularly in light of developmental delay, warrant prolonged EEG studies for spell characterization.

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From UT Southwestern, Austin, TX. All authors are currently with UT Austin, TX.

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SECTION 2

Just before her first visit to our office, the patient had a more prominent episode that began with a fall followed by apnea and cyanosis. As observed in prior events, there was a 2- to 3-minute period of unresponsiveness; however, distinct from others, this event was followed by a 10-minute recovery period. A 3-day EEG at this time revealed rare but obvious 150–200 μV bursts of 2–2.5 Hz generalized spike and wave activity during sleep; no clinical events were captured. The suspicious nature of this event along with interictal epileptiform activity prompted treatment with lamotrigine (Lamictal; GlaxoSmithKline, Research Triangle Park, NC). Her family reported that after starting lamotrigine the child was more alert, attentive, and made developmental gains, more notably in expressive than receptive language skills. The family reported that milder episodes of unresponsiveness and dystonic posturing continued intermittently. In addition to presumed seizures, the mother described transient episodes of poor balance and slightly unstable gait that self-resolved within hours to days.

Questions for consideration:

1. How does the differential diagnosis broaden in an ataxic toddler with a history of seizures and dystonic posturing?
2. Is there a unifying diagnosis?
3. What further workup should be performed?

It is important to recognize the evolution of symptoms as a child develops. Previously reported poor coordination has now become a more obvious intermittent ataxia. With the addition of episodic, reversible ataxia, the diagnostic considerations broaden to include vitamin deficiencies, neuroblastoma, various metabolic disorders, and genetic ataxias.

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At 3 years old, the patient was hospitalized during a severe ataxic episode that gradually resolved over 10 days. Repeat MRI was normal and EEG showed the same interictal generalized spike and wave activity during sleep. Lactate, ammonia, vitamins B_{12} and E, urine organic acids, urine catecholamines, and α-fetoprotein were all within normal limits. Workup for hereditary ataxias was negative. Lumbar puncture was performed to collect CSF neurotransmitters and a glucose level. Studies revealed normal levels of neurotransmitters and a low CSF glucose of 28 (normal 45–80 mg/dL) compared to near simultaneous serum glucose of 89.

Sequence analysis of the *SLC2A1* gene coding region revealed an in-frame deletion, confirming the diagnosis of GLUT1 deficiency syndrome. One of the characteristic features of the GLUT-1 transporter is a 5-residue motif RXGRR (where X is any amino acid) present in the cytoplasmic loops that connect transmembrane (TM) domains 8 and 9.[1] The mutation seen in our patient occurs on the boundary of TM domain 8 and the cytoplasmic loop. Considering the location of the deletion within this highly conserved sequence, this mutation likely alters the function of the transporter, resulting in the symptoms noted in our patient.

This is a novel mutation not previously reported. Both parents' *GLUT1* genes were sequenced, with normal results confirming the de novo occurrence of the mutation in the patient. Review of the literature and listed genetic mutations to date indicate no other reported pathogenic in-frame deletions within *SLC2A1*.

Table Common symptoms associated with GLUT1-DS phenotypes

GLUT1-DS phenotypes	Symptoms
Classical	Seizures (focal, apneic/cyanotic, abnormal eye movements, absence); may transform or generalize over time
Early onset (<2 y)	Mild to severe developmental delay (primarily speech, dysarthria)
Late onset (>2 y)	Ataxia (C/P)
	Dystonia (C/P)
	Chorea (C/P)
Nonclassical	Mild to severe developmental delay
≥3 y	Ataxia (C/P)
	Dystonia (C/P)
	Chorea (C/P)
Adult onset	Mild/infrequent seizures (myoclonic or generalized tonic-clonic)
Adolescence/early adulthood	Paroxysmal exercise-induced dyskinesia

Abbreviation: C/P = continuous or paroxysmal (some patients have continuous symptoms with paroxysmal worsening).
The table outlines the known phenotypes of GLUT1 deficiency syndrome (GLUT1-DS). The classical presentation is the most common, with the majority of patients presenting before 2 years of age. There is a late-onset form wherein patients develop symptoms after 2 years and have been noted to have less severe developmental delay than their younger counterparts. The nonclassical and adult-onset types are significantly less common.[4] In adult-onset GLUT1-DS, symptoms are typically brought on by stress, fatigue, and fasting.[10] Column 2 is presented in descending order of reported frequency.[4]

DISCUSSION Classic GLUT1 deficiency syndrome (GLUT1-DS) can present with a variety of symptoms including infantile seizures, developmental delay, movement disorders, or ataxia.[2] The table illustrates many of the features associated with the 3 known phenotypes of GLUT1-DS. The symptoms result from decreased CSF glucose due to a mutation in the *SLC2A1* gene, which encodes a membrane-spanning protein that transports glucose across the blood–brain barrier.

GLUT1-DS frequently does not present until the later part of infancy, which may be due to the fact that in the neonatal period ketones are more readily available as a source for energy metabolism in the brain. As cerebral glucose uptake increases during childhood, it is postulated that inadequate glucose transport to neurons results in impaired cerebral metabolism and disruption of thalamocortical development.[3] In one retrospective study of 46 patients with early-onset, classical GLUT1-DS, average CSF glucose was 1.7 mmol/L (30 mg/dL) with a CSF: serum glucose ratio of 0.35.[4] The average time to diagnosis of patients in this study was 6 1/2 years after the onset of symptoms. Seizure presentation varies greatly, including cyanotic spells, atypical absence, atonic, and generalized tonic-clonic seizures, among others.[2] Extent of intellectual disability correlates with the severity of hypoglycorrhachia.[4]

Since the identification of the syndrome in 1991, approximately 200 patients have been reported, of whom 70%–80% have one of a variety of mutations within the *SLC2A1* gene.[5] In a 2005 review,[6] 14 of 16 patients in whom genetic analysis was performed had novel genetic mutations within *SLC2A1*. In that article, Wang et al.[6] proposed 5 different phenotypes based on the extent of residual function of GLUT1, ranging from minimal to lethal. In 2010, Leen et al.[3] expanded upon this hypothesis by demonstrating that patients with nonsense, frameshift, and multiple exon deletions had lower CSF glucose concentrations and frequently more severe presentation than those with missense mutations. To date, however, no exact correlation between genotype and phenotype has been discerned. Even among patients with identical mutations, there remains significant phenotypic variance. This variability in presentation and severity likely reflects influence of other genes related to the function of *SLC2A1*.[5]

In GLUT1-DS, neurons utilize ketones as a source of energy instead of glucose. The ketogenic diet (KD) functions by limiting carbohydrates and

increasing fat content, thereby promoting ketone body formation. A variety of ketogenic dietary regimens exist, several of which have been shown to be effective. The KD is frequently used as supplementary or second-line treatment for intractable epilepsy; however, in GLUT1-DS it is the primary treatment since an alternate source of fuel for the brain is necessary to prevent symptoms.

As long as adequate ketosis is maintained, seizure control can frequently be achieved without anticonvulsants.[7] In one retrospective study of 37 patients with GLUT1-DS with epilepsy, 62% acquired complete seizure control and another 24% had a reduction in frequency.[4] The KD has also been shown to be effective in decreasing the frequency/severity of movement disorders.[4] Although a baseline level of delay is expected in all children, adequate treatment with the KD allows for greater developmental progress. Early recognition of GLUT1-DS optimizes this possibility. Of significance, the KD in rat models has been shown to decrease brain growth and impair visual-spatial learning compared to controls.[8] Studies in humans are necessary to further understand the potential effects on memory. Additional long-term complications of the diet are currently being investigated, including dyslipidemia due to high fat content and poor growth due to limited protein intake.[9] The extent of seizure control is highly dependent on the patient's compliance with the diet. The difference in fat: carbohydrate + protein ratio affects the palatability of the diet, which can influence adherence.

Our patient, now 5 ½ years old, has been seizure-free for 22 months since starting on a KD. She was initially weaned off lamotrigine but became irritable, so was restarted on a lower dose for mood stability. During this time, she has had noticeable improvement in her language and motor skills. Recent neuropsychological evaluation using the Adaptive Behavior Assessment System–II suggested a developmental functioning in the 3–5 years range, with most simple tasks being age-appropriate. She displayed weakness with complex tasks involving memory, long-term attention, and multimodal learning.

The presentation of GLUT1 deficiency syndrome can often be subtle. Developmental delay may be mild, and other associated signs/symptoms are highly variable. Detection of seizures may be difficult; therefore, prolonged EEG may be helpful in confirming ictal events. CSF studies with concurrent serum glucose levels should be obtained to establish a diagnosis. It is important to consider this metabolic disorder in infants and children with a constellation of refractory paroxysmal events, gait disturbance, and involuntary movements, especially when symptoms worsen with illness or fasting. Early recognition of GLUT1-DS and appropriate treatment can allow for a much higher quality of life.

AUTHOR CONTRIBUTIONS

Sonali T. Sen: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. Karen Keough: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, study supervision. James Gibson: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval.

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DISCLOSURE

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