

Current Literature

In Clinical Science



A Sweet Cause of Toddlers With Absence Seizures

Early Onset Absence Epilepsy: 1 in 10 Cases is Caused by GLUT1 Deficiency.

Arsov T, Mullen SA, Damiano JA, Lawrence KM, Huh LL, Nolan M, Young H, Thouin A, Dahl HM, Berkovic SF, Crompton DE, Sadleir LG, Scheffer IE. *Epilepsia* 2012;53:e204–e207.

Glucose transporter 1 (GLUT1) deficiency caused by mutations of SLC2A1 is an increasingly recognized cause of genetic generalized epilepsy. We previously reported that > 10% (4/34) of a cohort with early onset absence epilepsy (EOAE) had GLUT1 deficiency. This study uses a new cohort of 55 patients with EOAE to confirm that finding. Patients with typical absence seizures beginning before 4 years of age were screened for solute carrier family 2 (facilitated glucose transporter), member 1 (SLC2A1) mutations or deletions. All had generalized spike-waves on electroencephalography (EEG). Those with tonic and/or atonic seizures were excluded. Mutations were found in 7 (13%) of 55 cases, including five missense mutations, an in-frame deletion leading to loss of a single amino acid, and a deletion spanning two exons. Over both studies, 11 (12%) of 89 probands with EOAE have GLUT1 deficiency. Given the major treatment and genetic counseling implications, this study confirms that SLC2A1 mutational analysis should be strongly considered in EOAE.

Commentary

Early-onset absence epilepsy (EOAE), or the onset of absence seizures at an age less than 4 years, may be different than classic childhood absence epilepsy (1). Seizures can be more atypical and require anticonvulsants in polypharmacy (2). Although less common than typical childhood absence epilepsy, children with EOAE can comprise a significant portion of a referral pediatric epilepsy practice.

Recent evidence has suggested that some patients with EOAE may have GLUT1 (glucose transporter 1) deficiency as the cause of their epilepsy (3–5). Although this concept has gained in popularity in the past few years, it was first formally proposed as a possibility by Dr. Larry Hirsch in an editorial (6). Dr. Arsov and the group from the Epilepsy Research Centre at the University of Melbourne have been the major researchers adding to this evolving GLUT1 story since 2009, with nearly annual publications linking the two conditions (3–5).

The spectrum of GLUT1 deficiency continues to expand rapidly, largely due in part to the widespread availability of the genetic test SLC2A1 (solute carrier family 2, member 1). This serum test is certainly simpler to obtain than the more cumbersome lumbar puncture previously required for diagnosis. As a result, GLUT1 has been recently associated with conditions other than epilepsy, including paroxysmal exertional dyskinesia, alternating hemiplegia of childhood, hemolytic anemia, and paroxysmal choreoathetosis with spasticity (7).

In 2009, Suls and colleagues started their work by reporting the results of screening 34 children with EOAE. They

identified 4 (12%) with GLUT1 deficiency, ages 7 to 28 years (3). The following year, two families comprised of 15 subjects with SLC2A1 were then published, of which 10 had absence-type epilepsy (4). This current publication in *Epilepsia* by the same group was designed to confirm the 2009 study results and determine the incidence of SLC2A1 mutations in another, slightly larger (55 patients) cohort with EOAE (5).

Surprisingly, results were nearly identical with 7 of 55 (13%) having SLC2A1 mutations as a cause of their EOAE. Six of 7 were males, and the onset was typically 2 to 3 years of age. Limited information was provided about any clinical features that may have provided a clue to the diagnosis of GLUT1, such as sensitivity to carbohydrates; however, the presence of intellectual disability was seen in half, movement disorder in one, and a CSF/plasma glucose ratio < 0.45 in none.

Combining both EOAE studies by the Australia group, 11 of 89 (12%) with EOAE were found to have GLUT1 deficiency (3, 5). This is quite striking, and I agree with their statement that these findings may have “major treatment and genetic counseling implications” (5). Recognizing that there exists some controversy about this 10% prevalence rate—with a multicenter Italian series recently finding no one with SLC2A1 mutations in a cohort of 84 children—consideration of testing all patients with EOAE still appears warranted due to the low risk and potentially high yield (8).

What was perhaps the most disappointing was the low implementation of dietary management for these children, despite the authors appropriately stating in their discussions that “the ketogenic diet is the treatment of choice for GLUT1 encephalopathy” (3) and “earlier consideration of the ketogenic diet may lead to seizure control and improved cognitive outcome” (5). In all three series combined, only 4 of 21 (19%) with absence epilepsy were treated with the ketogenic diet (3–5).



Seven children in these series were reported as still having absence seizures despite at times “multiple medications,” yet they were not receiving the widely recognized treatment of first choice. It is not stated why dietary management was not utilized, so perhaps some parents or subjects refused or the diet was not feasible for financial or logistical reasons. Dietary management can be very helpful for absence epilepsy (either EOAE or more classic cases) and should be discussed whenever a patient (child or adult) becomes medication-resistant, especially for those with GLUT1 deficiency (9).

The next few years will be very interesting in the field of GLUT1 deficiency. What other epilepsies will be revealed as possibly due to GLUT1? As the SLC2A1 genetic test becomes more widely available and less expensive, will other paroxysmal neurologic conditions—such as migraine, multiple sclerosis, or mitochondrial disorders—be etiologically linked in some cases to this mutation? Lastly, would a positive SLC2A1 result, identified early for a child with epilepsy, lead to first-line use of a ketogenic diet? This would seem logical and in many ways perhaps the only reason to test for SLC2A1. Should the natural course of these epilepsies be improved by such early dietary management, then this genetic test could have important implications.

by Eric H. Kossoff, MD

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