Glucose Transporter 1 Deficiency as a Treatable Cause of Myoclonic Astatic Epilepsy

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Objective: To determine if a significant proportion of patients with myoclonic-astatic epilepsy (MAE) have glucose transporter 1 (GLUT1) deficiency.

Design: Genetic analysis.

Setting: Ambulatory and hospitalized care.

Patients: Eighty-four unrelated probands with MAE were phenotyped and SLC2A1 was sequenced and analyzed by multiplex ligation-dependent probe amplification. Any identified mutations were then screened in controls.

Main Outcome Measure: Any SLC2A1 mutations.

Results: Four of 84 probands with MAE had a mutation of SLC2A1 on sequencing. Multiplex ligation-dependent probe amplification analysis did not reveal any genomic rearrangements in 75 of the remaining cases; 5 could not be tested. Two patients with MAE with SLC2A1 mutations also developed paroxysmal exertional dyskinesia in childhood.

Conclusions: Five percent of our patients with MAE had SLC2A1 mutations, suggesting that patients with MAE should be tested for GLUT1 deficiency. Diagnosis of GLUT1 deficiency is a strong indication for early use of the ketogenic diet, which may substantially improve outcome of this severe disorder.

Mycoclonic-Astatic Epilepsy (MAE), classified among the generalized epilepsies, is characterized by generalized seizures that begin in early to mid-childhood, typically with a stormy onset including myoclonic, myoclonic-atonic, absence, and generalized tonic-clonic seizures and nonconvulsive status epilepticus.1,2 The electroencephalogram (EEG) shows generalized spike- or polyspike-wave activity at more than 2.5 Hz without generalized paroxysmal fast activity or focal spikes. Early development is usually normal; however, outcome varies from an encephalopathic course to normal intellect. Approximately 50% of patients with MAE improve on the ketogenic diet (KD).3,4

The KD is also the treatment of choice for individuals with glucose transporter 1 (GLUT1) encephalopathy due to mutations in the gene solute carrier family 2 (facilitated glucose transporter), member 1 (SLC2A1), which encodes GLUT1. Glucose transporter 1 is the main glucose transporter across the blood-brain barrier.5 Mutations of SLC2A1 cause GLUT1 encephalopathy, an early-childhood metabolic disorder with intractable epilepsy, cognitive impairment, and movement disorders.3 The KD produces ketone bodies that diffuse across the blood-brain barrier. Diffusion is facilitated by a monocarboxylic acid transporter and therefore bypasses the GLUT1 defect; ketone bodies are thus thought to provide an alternative energy source for brain metabolism.6-8

The spectrum of disease associated with GLUT1 deficiency is expanding. Autosomal dominant families with paroxysmal exertional dyskinesia (PED) have been described; some family members also had seizures and cognitive impairment.9 Recently, we reported that 10% of patients with early-onset absence epilepsy beginning at younger than 4 years had GLUT1 deficiency.10 Thus, SLC2A1 mutations are predominantly associated with generalized seizures, in most cases manifesting as absence seizures or as myoclonus.11,12 Seizures may be the presenting and predominant symptom bringing the child to medical attention.

We hypothesized that GLUT1 deficiency may cause MAE given their similar epilepsy phenotype with absence and myoclonic seizures in early life and the shared responsiveness of MAE and GLUT1 deficiency to the KD.

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Table. Clinico-molecular Features of the Patients With MAE and GLUT1 Deficiency

<table>
<thead>
<tr>
<th>Patient/ Sex/ Age, y</th>
<th>Sz Onset</th>
<th>EEG Findings</th>
<th>AEDs/Sz Outcome</th>
<th>KD/ Age at Onset</th>
<th>Cognitive Features</th>
<th>Neurological Examination</th>
<th>Movement Disorder Onset</th>
<th>CSF to Blood Glucose Level Ratio</th>
<th>SLC2A1 Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/15 48 mo/ My, My-At</td>
<td>GS, GPSW</td>
<td>VPA + EST; 5 y</td>
<td>Yes/ 13.5 y</td>
<td>Normal early development, progressive regression; at 5 y WPSI FSIQ score 76; 6 y WPSI FSIQ score, 63; 7 y WPSI FSIQ score, 59; 13 y WISC-R FSIQ score &lt;40</td>
<td>Tremor, mild dystrophic speech</td>
<td>6 y PED &gt; lower limbs (&gt; R); Exercise; facial grimaces; duration 30-180 min; monthly frequency</td>
<td>Mild ID</td>
<td>35 mg/dL/NA</td>
<td>c.997T&gt;G; p.Arg333Trp parents, NA</td>
</tr>
<tr>
<td>2/M/4 24 mo/ My-At, My</td>
<td>GSW</td>
<td>VPA 1 y, sz-free</td>
<td>Yes/ 2.5 y</td>
<td>Mild motor and speech delay at 2 y and 2 mo (Griffiths score at 2 y, 62 and at 8 mo, 66)</td>
<td>Ataxia, dystrophic speech, poor motor performances, deceleration of head growth</td>
<td>None</td>
<td>32 mg/dL/0.42</td>
<td>c.1199G&gt;A; p.Arg400His de novo</td>
<td></td>
</tr>
<tr>
<td>3/M/2 48 mo/ At, Ab, GTCS, non-CSE</td>
<td>GSW</td>
<td>VPA + TPM; 4 y sz-free</td>
<td>No</td>
<td>Mild motor and speech delay, progressive regression to severe ID</td>
<td>Dysarthric speech, ataxia, poor motor performances</td>
<td>6-7 y PED &gt; lower limbs (&gt; L); Exercise</td>
<td>NA</td>
<td>37 mg/dL/0.42</td>
<td>c.997T&gt;G; p.Arg333Trp de novo</td>
</tr>
<tr>
<td>4/M/28 28 mo/ Ab, GTCS, non-CSE</td>
<td>GSW</td>
<td>VPA + LTG; 4 y sz-free</td>
<td>No</td>
<td>Normal</td>
<td>Normal</td>
<td>None</td>
<td>NA</td>
<td>971C&gt;T; p.Ser324Leu maternal</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Ab, absence seizures; AED, antiepileptic drug; At, atonic seizures; CSE, convulsive status epilepticus; CSF, cerebrospinal fluid; EEG, electroencephalogram; EST, ethosuximide; FSIQ, full-scale IQ; GLUT1, glucose transporter 1; GPSW, generalized polyspike-wave; Griffiths, Griffiths Mental Developmental Scales; GSW, generalized spike-wave; GTCS, generalized tonic-clonic seizures; ID, intellectual disability; KD, ketogenic diet; L, left; LTG, lamotrigine; M, male; MAE, myoclonic-astatic epilepsy; My, myoclonic seizures; My-At, myoclonic-atonic seizures; NA, not available; PED, paroxysmal exertional dyskinesia; R, right; Sz, seizure; TPM, topiramate; VPA, valproic acid; WISC-R, Wechsler Intelligence Scale for Children–Revised; WPSI, Washington Psycho-Social Seizure Inventory; >, predominant; ↑, increased.

METHODS

We obtained a detailed history for the patients with MAE, who underwent examination. Where possible, video EEG recordings were obtained and all available EEG and imaging studies were reviewed. All recruitment was approved by the relevant ethics committees.

A syndrome diagnosis of MAE was made and patients were divided into those fulfilling a narrow or a broad definition of MAE. The narrow group was defined as having onset of afebrile seizures between 1 and 5 years of age in a previously healthy child who presented with multiple seizure types including at least 1 of myoclonic or myoclonic-atonic seizures with or without generalized tonic-clonic seizures or atonic or absence seizures, accompanied by gen-

RESULTS

A total of 84 patients were tested; 67 fulfilled the narrow definition and 17 fit the broad definition of MAE. Three cases with a narrow MAE definition and a further case with a broad definition had SLC2A1 mutations (4 of 84; 5%). The clinico-molecular details are summarized in the Table. Mutations in the 3 patients with a narrow MAE definition (patients 1-3) (Table) were missense changes: 2 were de novo and no parental DNA was available for 1 patient. The c.997C>T mutation, in exon 8, changes an arginine to a tryptophan residue (p.Arg333Trp) and appears to have arisen independently in 2 patients (patients 1 and 3). Patient 2 had a mutation in exon 9 (c.1199G>A), changing an arginine to a histidine residue (p.Arg400His). The mutation in the patient drawn from the broad definition cohort (patient 4) has been previously reported as part of a family study; however, this case was ascertained independently as part of the cohort study of MAE. The SLC2A1 mutation is in exon 7 (c.971C>T), changing a serine to a leucine residue (p.Ser324Leu). Patients 1 to 3 (narrow MAE cohort) had an almost identical epilepsy phenotype consisting of multiple seizure types, including myoclonic-atonic seizures, and cognitive decline, resulting in severe intellectual disability in patients 1 and 3 and mild disability in patient 2. Patients 1 and 3 developed PED, often triggered by walking, exercise, and tiredness (Table). The PED did not appear until 6 years of age in both

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Glucose transporter 1 deficiency is an important and treatable cause of MAE, being present in around 5% of patients in our series. Glucose transporter 1 encephalopathy is associated with seizure types that share some features with MAE. Although the early seizures are usually focal in GLUT1 encephalopathy, by 2 years of age the most common pattern is a combination of generalized tonic-clonic seizures and absence, myoclonic, and atonic seizures associated with generalized spike-wave on EEG. However, unlike MAE, seizures occur in the context of abnormal early development. In addition to intellectual disability and refractory seizures, GLUT1 encephalopathy is associated with a complex motor disorder with pyramidal and extrapyramidal features as well as microcephaly in some cases.

Familial cases of GLUT1 deficiency may also resemble MAE. The original 2 reports of familial GLUT1 deficiency were of sibling pairs with classic GLUT1 encephalopathy and a more mildly affected parent. In both families, the affected parent had seizures and onset age consistent with MAE, although full details were not provided. A further family with 2 siblings had prolonged periods of nonconvulsive status combined with atonic seizures, and in 1 case, myoclonic elements were also reported.

In 3 of our 4 patients (Table) (patients 1, 3, and 4), the molecular diagnosis of GLUT1 deficiency was delayed from epilepsy onset. In proband 4, the diagnosis was made post mortem. In probands 1 and 3, the diagnosis was delayed until 6 years of age; prior to this, both boys had the epilepsy phenotype of classic MAE. Progressive slow cognitive decline and mild motor impairment were attributed to seizures and the use of antiepileptic drugs.

The Arg333Trp mutation, identified in patients 1 and 3, has already been described in several patients, confirming a hot spot. Although details of the epilepsy in these cases are incomplete, the phenotypes appear to vary from classic encephalopathy with infantile seizures and microcephaly to epilepsy consistent with MAE. Mutagenesis studies on both the arginine residues (Arg 333 and Arg400) involved in the mutations in patients 1, 2, and 3 have been published and showed reduced glucose transport due to interference with glucose-induced conformational changes in the GLUT1 protein. The Ser324Leu mutation detected in patient 4 was previously reported as a familial mutation and deficient glucose transport demonstrated following expression in Xenopus oocytes.

The example of patient 2 and the excellent response of both epilepsy and development to initiation of the KD suggests that earlier diagnosis may have a large impact on final outcome. Two patients (patients 1 and 3) with the same mutation arising independently did develop PED, so that a clinical diagnosis of GLUT1 deficiency might have been made, but this was not until 6 years of age in either case, missing the opportunity for early initiation of the KD that a molecular diagnosis might have offered. Therefore, delaying testing for SLC2A1 mutations until PED has emerged will miss cases, delay diagnosis, and potentially adversely affect long-term outcome. Determining the level of glucose in the cerebrospinal fluid may provide additional information that can confirm pathogenicity of the mutation. Lumbar puncture is a significantly invasive procedure, particularly in infants and young children and especially compared with blood tests for genetic sequencing. Also, although results of lumbar puncture were abnormal in these cases, in other cases of GLUT1 deficiency outside of the classic encephalopathy cerebrospinal fluid glucose results have been within the normal range. Whether lumbar puncture or sequencing should form the first-line test for GLUT1 deficiency in MAE thus remains an open question.

Cerebral fluorodeoxyglucose F 18 positron emission tomography of patients with GLUT1 deficiency syndrome shows changes of global cortical hypometabolism, more severe in the mesial temporal regions and thalami, and a relative hypermetabolism in the basal ganglia. The sensitivity and specificity of positron emission tomography for the diagnosis of GLUT1 deficiency is, however, unknown and positron emission tomography requires a general anesthetic in infants and young children.

The epilepsy in all 4 patients was indistinguishable from the rest of the MAE cohort. Glucose transporter 1 deficiency was identified in both the narrow and broad definitions of MAE, illustrating that epilepsy syndromes are not precise entities and different etiologies may result in the same phenotype. Overall, GLUT1 deficiency should be suspected in all patients with MAE, and clinical or EEG features cannot be used to exclude the diagnosis. On the other hand, the presence of PED should heighten suspicion of GLUT1 deficiency.

Deletions, duplications, or amplifications involving 1 or more exons of the SLC2A1 gene do not seem to be associated with the MAE phenotype. It is likely that such genomic abnormalities are mostly associated with classic GLUT1 encephalopathy.

This work suggests that sequencing of SLC2A1 should become part of the diagnostic workup for MAE. The likelihood of 1 in 20 MAE cases being due to GLUT1 deficiency is a relatively modest diagnostic rate but the im-
plications for treatment are major. The KD can be expected to control seizures. Just as importantly, the KD is likely to improve cognitive outcome as GLUT1 deficiency is often associated with intellectual impairment arising from the metabolic defect. Such individualized treatment of the pathological basis of epilepsy is a significant advance in this often devastating disorder.

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REFERENCES