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.

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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 atomic or absence seizures, accompanied by generalized tonic-clonic seizures; ID, intellectual disability; KD, ketogenic diet; L, left; LIGT, lamotrigine; M, male; MAE, myoclonic-astatic epilepsy; M-A-T, 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; >; predominantly; ↑, increased.

Abbreviations: Ab, absence seizures; AED, antiepileptic drug; At, atonic seizures; CSE, nonconvulsive status epilepticus; CSF, cerebrospinal fluid; EEG, electroencephalogram; ESM, 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; LIGT, lamotrigine; M, male; MAE, myoclonic-astatic epilepsy; My, myoclonic seizures; My-A-T, 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; >; predominantly; ↑, 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 atomic or absence seizures, accompanied by generalized spike- or polyspike-wave discharges on EEG. The broad definition allowed a wider onset age from 7 months to 6 years and also included myoclonic-atonic seizures or atonic or absence seizures, accompanied by generalized spike- or polyspike-wave discharges on EEG. The broad group had a broader age range for onset, but still required afebrile seizures.

**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.
cases, at least 3 years after their epilepsy began and well after cognitive decline had commenced. Patient 2 was diagnosed with GLUT1 deficiency syndrome at 2 years of age, 12 months after epilepsy onset. This early diagnosis and prompt initiation of the KD might be the reason why this child has not experienced progressive cognitive decline. Patient 4 had the onset of frequent atonic and absence seizures at 4 years of age. A progressive epileptic encephalopathy ensued with eventual mild intellectual disability. Seizures were refractory up until his accidental death at 28 years of age.

In patients 1, 2, and 3, results of a fasting lumbar puncture showed a reduced glucose level in the cerebrospinal fluid (32-37 mg/dL) with a lowered cerebrospinal fluid to blood glucose ratio of 0.42 in the 2 patients in whom it was available (Table). These findings confirm that SLC2A1 mutations cause an impairment of glucose transport from the bloodstream across the blood-brain barrier to the central nervous system due to GLUT1 deficiency.

Multiplex ligation-dependent probe amplification screening of the 75 patients with MAE who were mutation negative on sequencing failed to show deletions, duplications, or amplifications of the SLC2A1 gene.

**COMMENT**

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 age years; 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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