Diagnosing Glucose Transporter 1 Deficiency at Initial Presentation Facilitates Early Treatment

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Objective To profile the initial clinical events of glucose transporter 1 deficiency syndrome (Glut1 DS) in order to facilitate the earliest possible diagnosis.

Study design We retrospectively reviewed 133 patients with Glut1 DS from a single institution. Family interviews and medical record reviews identified the first clinical event(s) reported by the caregivers.

Results Average age of the first event was 8.15 ± 11.9 months (range: 0.01-81). Ninety-one patients experienced the first symptom before age 6 months (68%). Thirty-three additional patients (25%) presented before age 2 years. Only 9 patients (7%), reported the first event after age 2 years. Seizures were the most common first event (n = 81, 61%), followed by eye movement abnormalities (n = 51, 38%) and changes in muscle strength and tone (n = 30, 22%). Eye movement abnormalities, lower cerebrospinal fluid glucose values, and lower Columbia Neurological Scores correlated with earlier onset of the first event (r: −0.17, 0.22, and 0.25 respectively, $P < .05$). There was no correlation with age of first event and red blood cell glucose uptake or mutation type.

Conclusions Glut1 DS is a treatable cause of infantile onset encephalopathy. Health care providers should recognize the wide spectrum of paroxysmal events that herald the clinical onset of Glut1 DS in early infancy to facilitate prompt diagnosis, immediate treatment, and improved long-term outcome. *(J Pediatr 2016;171:220-6)*.

Glucose transporter 1 deficiency syndrome (Glut1 DS) is a unique genetic syndrome caused by insufficient transport of glucose from the blood to the brain.[1] Paroxysmal events in early infancy, typically witnessed by parents and other caregivers, herald the clinical onset of this treatable condition. Other clinical features, such as deceleration of head growth, acquired microcephaly, spasticity, ataxia, dystonia, dysarthria, and intellectual disability, emerge later in infancy and childhood.[2,3]

Seizures are the most common early symptom of Glut1 DS, often bringing the infant to medical attention.[4,5] Generalized seizures are the most frequent seizure type, including myoclonic, absence, and tonic-clonic seizures. Infantile spasms are rare. Focal seizures also are seen in the younger age group, and, most specifically, in infancy.[4,5] Hypoglycorrhachia is the laboratory hallmark of the diagnosis, but this biomarker is not appreciated until after the onset of symptoms, and only if a lumbar puncture is performed. Seldom, however, is a diagnostic lumbar puncture performed to investigate such clinical symptoms. As a result, there often is a significant time-lag between the onset of clinical symptoms and the recognition of this key cerebrospinal fluid (CSF) biomarker.[4] Years, in fact, may pass before the correct diagnosis is made and appropriate treatment is initiated.[4] In addition, there are some patients who present clinically with the features of Glut1 DS, but *SLC2A1* gene sequencing for a disease-causing mutation is negative.[6,7] These patients also may have hypoglycorrhachia and may benefit from treatment with a ketogenic diet. The disease mechanism in this patient cohort remains unknown presently.[7]

Early diagnosis and prompt treatment of patients with Glut1 DS is important for prognosis.[3,8] The ketogenic diet remains the most effective treatment for Glut1 DS. Treatment in infancy provides ketones to supplement glucose as an oxidizable metabolic fuel to meet the heightened demands of the young, immature, growing brain. If the ketogenic diet provides neuroprotection, it stands to reason that early treatment would be preferable.

Early diagnosis also requires recognition of initial clinical symptoms. Therefore, in this study, our primary goal is to identify the initial clinical signs of Glut1 DS as determined by the patient caregivers. We hope that early recognition of initial symptoms will facilitate prompt treatment of this syndrome, thereby mitigating cerebral energy failure during the critical period of early brain growth and development.

CNS	Columbia Neurologic Score
CSF	Cerebrospinal fluid
Glut1 DS	Glucose transporter 1 deficiency syndrome
RBC	Red blood cell

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Methods

From 1989-2012, data from 138 research patients were collected by the staff of the Colleen Giblin Research Laboratory at the Columbia University Medical Center. The study was approved by the Columbia University Institutional Review Board. Informed consent was obtained from patients and their parents.

This study was conducted by retrospective chart review. All patients had a clinical phenotype that was consistent with Glut1 DS. Most patients also met the full diagnostic criteria for Glut 1 DS: hypoglycorrhachia, abnormally low red blood cell (RBC) glucose uptake, and disease-causing mutation in the *SLC2A1* gene.[6,9]

The demographic information, first event, age of onset, age at the time of diagnosis, history of seizures or other cardinal features, and diagnostic test results including CSF glucose level, RBC uptake, and genetic analysis were reviewed. The Columbia Neurologic Score (CNS) was used to assess the phenotypic severity of patients diagnosed with Glut1 DS.[10,11] This is a semiquantitative tool that scores the following physical examination domains: (1) height, weight, and head circumference; (2) general medical examination; (3) funduscopic examination; (4) cranial nerves; (5) stance and gait; (6) involuntary movements; (7) sensation; (8) cerebellar function; (9) muscle bulk, tone, and strength; (10) tendon reflexes; (11) Babinski sign; and (12) other findings. Results for each of these domains were scored as "normal" or "abnormal" and summarized in the CNS ranging from 0-76, with 76 being perfect. It was previously shown that this instrument has good interrater reliability and correlates with other measures of disease severity. Based on CNS scores, the neurologic phenotype was described as severe (CNS 40-49); moderate (CNS 50-59); or mild (CNS 60-69). The minimal phenotype (CNS 70-76) merged with the control subjects.[11]

Family interviews and medical records from local physicians were used to identify the time and type of first neurologic event that brought the patient to medical attention. Based on the description of first symptoms, 2 symptomatic groups were created: (1) patients presenting with "motor manifestations"; and (2) patients presenting with "behavioral changes." Subgroups were created within the 2 groups to summarize the clinical events. In group 1, the several subgroups included frank seizures, abnormal eye movements, changes in muscle tone or strength, and involuntary movements characterized by motor manifestations; in group 2 the subgroups included changes in breathing pattern, disturbed alertness, autonomic features, and vocalizations.

Results

Clinical information was available from 133 patients, 68 of whom were male (Table I). Mean age at the time of the diagnosis of Glut1 DS was 7.1 ± SD 8.8 years (range: 0.2-31 years). CSF glucose concentration was not available in 5 patients. CSF glucose was 32 ± 4.8 mg/dL (range: 14-54 mg/dL). Four patients had CSF glucose >40 mg/dL (41-54 mg/dL). Pathogenic *GLUT1* mutations were demonstrated by *SLC2A1* gene sequence in 122 patients.[9] The majority of patients had missense (n = 57, 46%) or deletion (n = 43, 35%) mutations, followed in decreasing order by nonsense (n = 9), splice site (n = 8), and insertion (n = 5) mutations. RBC glucose uptake results were available in 124 patients. The average uptake value was 54.9% ± 12% (range: 31%-119%).

Table I. Clinical features of patients with Glut1 DS (n = 133)

Clinical features	
Age of first event, mo, mean ± SD	8.15 ± 11.9 (0.03-81)
Age at diagnosis of Glut1 DS, y, mean ± SD	7.1 ± 8.8 (0.2-31)
Sex: male/female	68/65
CNS, mean ± SD	56 ± 8.7 (40-73)
First event (n)	
Motor findings	128
Behavioral changes	39
First event (n at each epoch)	
0-6 mo	91
7-12 mo	16
13-24 mo	17
>24 mo	9
CSF glucose, mg/dL, mean ± SD	32 ± 4.8 (14-54)
RBC glucose uptake, %, mean ± SD	55 ± 12 (31-119)
Genotype (n)	
Missense mutation	57
Nonsense mutation	9
Deletion	43
Splice site mutation	8
Insertion	5

CNS is an established outcome measure of the clinical neurologic examination with scores ranging from 0-76. The normal range is 70-76. Minimally affected patients overlap with the normal control range; mildly affected patients 60-69; moderately affected patients 50-59; and severely affected patients 40-49. The CNS correlates with the RBC glucose uptake % as a surrogate of haploinsufficiency.

Age of onset for the first event was 8.15 ± 11.9 months (range: 0.01-81). More than one-half of the patients experienced their first event before age 6 months (n = 91; 68%). An additional 33 patients (25%) presented with their first event before age 2 years (Figure 1). Only 9 patients (7%) had first events reported after age 2 years.

Initial clinical symptoms reported by caregivers are shown in Table II. In an effort to capture the entire spectrum of initial clinical symptoms, the original caregivers' descriptions were recorded "verbatim." The categories of clinical symptoms in the 2 groups are summarized in Figure 2.

Motor symptoms were reported in 128 (96%) patients and behavioral changes in 39 (29%). Caregivers reported more than 1 clinical event in the majority of patients (n = 71, 53%).

Seizures were the most common first event, reported in 81 children (61%). Based on the clinical description, seizures represented a broad range from blank staring, to myoclonus, head drop, tonic stiffening, clonic activity of 1 or more extremities, and generalized tonic-clonic seizures. Age of seizure onset was 8.5 ± 10.5 months (range: 0.1-60). Most patients (n = 51, 63%) had seizures before age 6 months,