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GLUT1 deficiency syndrome as a cause of encephalopathy that includes cognitive disability, treatment-resistant infantile epilepsy and a complex movement disorder

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Abstract

Glucose transporter-1 (GLUT1) deficiency syndrome is caused by heterozygous mutations in the *SLC2A1* gene, resulting in impaired glucose transport into the brain. It is characterized by a low glucose concentration in the cerebrospinal fluid (hypoglycorrhachia) in the absence of hypoglycemia, in combination with low to normal lactate in the cerebrospinal fluid (CSF). It often results in treatment-resistant infantile epilepsy with progressive developmental disabilities and a complex movement disorder. Recognizing GLUT1 deficiency syndrome is important, since initiation of a ketogenic diet can reduce the frequency of seizures and the severity of the movement disorder. There can be a considerable delay in diagnosing GLUT1 deficiency syndrome, and this point is illustrated by the natural history of this disorder in a 21-year-old woman with severe, progressive neurological disabilities. Her encephalopathy consisted of treatment-resistant seizures, a complex movement disorder, progressive intellectual disability, and deceleration of her head growth after late infancy. Focused evaluation at age 21 revealed GLUT1 deficiency caused by a novel heterozygous missence mutation in exon 7 (c.938C > A; p.Ser313Try) in *SLC2A1* as the cause for her disabilities.

Keywords

Genetic encephalopathy; GLUT1 deficiency syndrome; *SLC2A1*; Absence seizures; Epidodic ataxia/dystonia; Cognitive disability; Treatment-resistant epilepsy; Ketogenic diet

1. Introduction

The classic patient with GLUT1 deficiency syndrome presents with infantile drug-resistant seizures, developmental delay, acquired microcephaly, hypotonia, spasticity, and a complex movement disorder consisting of ataxia and dystonia [9]. Herein we describe a 21-year-old woman with GLUT1 deficiency syndrome in whom the diagnosis was not made until age 21 years, allowing description of the natural history of this disorder throughout childhood. Early diagnosis is critical because it allows for treatment with a ketogenic diet, which reduces the frequency of seizures and dystonic movements that arise because of impaired glucose transport into the brain.

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2. Case report

This patient was born following a normal pregnancy labor and delivery, with normal birth growth parameters and Apgar scores. She was discharged shortly after delivery and remained healthy through early infancy. Family history was negative for anyone else with disabilities or genetic diseases, and there was no known consanquinity. At age 8 months, her head circumference was at the 40th percentile, with gradual deceleration of head growth noted thereafter. She developed strabismus at age 9 months, and had one 5 min tonic clonic seizure in association with otitis media at age 10 months. Her father had applied the insecticide chlorpirifos the night before she had this seizure, but her cholinesterase level was not depressed when she was evaluated for this seizure. Her strabismus was surgically repaired at age 15 months, and at 20 months a neurologist noted developmental delay and diagnosed a static encephalopathy with normal brain CT scan and chromosome analysis.

At age 29 months, she became unable to stand late in the day due to ataxia, which improved upon administration of sugar or food. Four or five alternating left or right-sided focal seizures occurred at age 31 months over a two-week period. She had an abnormal EEG showing 3 per second spike and slow wave discharges and a normal brain MRI. She was started on phenobarbital, which temporarily improved the seizures and episodic ataxia, and she received physical therapy, occupational therapy and speech therapy for severe expressive language delay. Her seizures recurred, so she was switched to carbamezepine at age 39 months, at which time an EEG was read as abnormal due to slow disorganized background and irregular spike slow wave discharges. A genetics evaluation revealed normal serum amino acids, normal urine organic acids, normal IgA, and normal Fragile X studies. Generalized seizures continued through age 5 years. She was switched to hydantoin at 44 months, with the addition of acetazolamide at 48 months, at which time a video EEG revealed subclinical bursts of spike slow wave discharges and excess slow background and disorganized rhythms for age.

At age 4.75 years, her neurologist noted global developmental delay with dysarthria, hyperactivity, and episodic ataxia in the evenings about once per week. Dystonia was documented at age 5.5 years, and she was started on amantadine. Her EMG was normal, and amblyopia was treated by patching her left eye. At age 6 years plasma very long chain fatty acids were normal, and plasma lactate was slightly elevated with normal CSF lactate and pyruvate (CSF glucose not done). Her worsening ataxia with signs of spasticity suggested she might have a progressive disorder. A continual video EEG remained abnormal showing modest asymmetry in background with more slowing over the right occiput, and sharp waves in the left temporal and frontal regions continuing during sleep. She was felt to have episodic dystonia/ataxia without any clear evidence of epileptic activity (Video S1, supplemental material online). Felbamate was not effective, and she was evaluated for a mitochondrial disorder. Repeat serum amino acids and urine organic acids were normal, plasma carnitine was normal, and muscle biopsy revealed low complex III activity (below 5% of normal control activity) suggesting an oxidative phosphorylation defect. A mitochondrial DNA point mutation screen was normal, and plasma coenzyme Q10 level was normal. Skin fibroblast pyruvate dehydrogenase complex assay was also normal. A lysosomal enzyme screen was also normal. CSF glucose was low at 33 mg/dl (normal 48–703 mg/dl), and repeat CSF glucose 10 months later was also low at 40 mg/dl, with normal peripheral blood glucose level normal at the time of the lumbar puncture. The significance of these findings was missed in 1994 and only appreciated in retrospect when her records were reviewed during the course of a lawsuit against the manufacturer of chlor-pyrifos at age 21 years.

Supplementary video related to this article can be found at doi: 10.1016/j.ejmg.2011.11.009.

By age 6.5 years, she was having episodes of headaches and screaming, with ataxia, uncontrollable behavior, and attention deficit hyperactivity disorder, which were treated with ethosux-imide and low doses of hydantoin. By age 7 years, she was using a wheelchair for increasing ataxia, global developmental delay, and the new onset of absence seizures. She had dysfunctional voiding with urinary incompetence and constipation. Her absence seizures were treated with ethosuximide, and her ataxia was treated with propranolol. Video EEG revealed intermittent spike and slow wave bursts that were not associated with clinical seizures, and repeat MRI showed mild asymmetry of choroidal fissures. Carbidopa-levodopa, clonazepam, and lamotrigine had no effect on the increasing frequency of her absence attacks, and she was treated with baclofen for increased tone in her lower extremities.

By age 13 years, the dystonic spells were occurring twice a week with multiple daily 20 s absence seizures, while her last generalized tonic clonic seizure was at age 5 years. Her EEG remained abnormal with slowing and disorganized background, and electroclinical seizures were correlated with her episodes of unresponsive staring and tongue or buccal movements. Increasing doses of zonisamide failed to control her multiple daily absence seizures, as did levetiracetram.

On exam at age 21 years her height was 168 cm, weight 84 kg and BMI 29.9, and head circumference was at the 3rd centile. She had multiple short daily absence seizures lasting seconds, multiple daily episodes of dystonia involving her head, neck and limbs, which increased with stress, exertion or illness, and her speech was dys-arthric, but she could carry on short conversations and follow simple commands. Her neurological evaluation revealed dystonia/ataxia affecting her lower extremities more than her upper extremities. Dystonia and ataxia were evident at rest as well as with activity. She could walk independently, but after a few steps, she began to lose her balance and required support to avoid falling. There were no abnormal eye movements, and limb power was close to normal, but her distal movements were clumsy, with legs more affected than arms (left more than right). Her deep tendon reflexes were equal throughout with bilateral plantar flexion and intact sensation.

She had moderately severe intellectual disability with significant deficits in adaptive functioning. At age 21 years, 9 months, she was unable to comprehend the task instructions for the Wechsler Adult Intelligence Scale-IV, so the Differential Ability Scales-II was administered. Her global cognitive ability (IQ) score was 37 with verbal cluster score <25, nonverbal reasoning score 28, and spatial score 34. Her age-equivalent scores ranged from 3 years, 7 months for language comprehension to 4 years, 4 months for visual motor integration to 6 years,1 month for single word expressive vocabulary. Her academic skills were at the pre-kindergarten level for reading, spelling and math, and her adaptive functioning was at 2 years, 9 months for motor skills, 4 years, 6 months for social/ communication skills, and 3 years, 5 months for personal living skills.

At age 21 years, a genetic evaluation revealed a normal chromosomal microarray, and sequence analysis of *SLC2A1* revealed a novel heterozygous missence mutation in exon 7 (c.938C > A; p.Ser313Try), which was predicted to have a deleterious effect on the glucose transporter. The mutation occurred in a location that is highly conserved across species, and red blood cell 3-0-methyl-D glucose uptake showed abnormally low uptake (70% of normal control), indicating an abnormality in glucose transport across the red cell membrane and confirming the diagnosis of GLUT1 deficiency syndrome. At age 15 years, 5 months, a modified Adkins diet was attempted to achieve better seizure control and for weight control, but it appeared to have little effect. There was no attempt to treat her with a ketogenic diet.

3. Discussion

The diagnosis of GLUT1 deficiency was delayed because these parents were convinced that their child's problems were caused by chlorpyrifos exposure. The true diagnosis of GLUT1 deficiency syndrome became known at age 21 years after sequence analysis of *SLC2A1* was performed during a civil lawsuit against the manufacturer of chlorpyrifos. The natural history of GLUT1 deficiency syndrome is demonstrated in this case report. The toxicity of chlorpyrifos is due primarily to inhibition of acetyl cholinesterase (AChE), and the effects of chlorpyrifos exposure in humans has been studied extensively [1–4]. Chronic non-occupational exposure to chlorpyrifos ranges from 0.0002 mg/kg-day (adults) to 0.0005 mg/kg-day (infants and small children). This level of exposure is insufficient to demonstrate any abnormalities in biomarkers of exposure in urine or blood, and developmental toxicity in laboratory animals never occurs at doses below maternal toxicity [6]. This patient's cholinesterase level within 48 h of her exposure was above the normal range, and she did not demonstrate any signs and symptoms of overexposure at the time of her initial hospitalization.

GLUT1 deficiency syndrome results from impaired glucose transport into the brain [5,7–10]. It can be associated with absence seizures and widely variable onset of symptoms [11,13], including paroxysmal exertion-induced dyskinesias [14,15]. The classic patient with GLUT1 deficiency syndrome presents with infantile drug-resistant seizures, developmental delay, acquired microcephaly, hypotonia, spasticity, and a complex movement disorder consisting of ataxia and dystonia [9].

Recently the clinical spectrum of GLUT1 deficiency syndrome has been broadened to include developmental delay and movement disorders without epilepsy [5], as well as familial and sporadic paroxysmal exercise-induced dyskinesia with or without epilepsy [12–14]. There are varying degrees of cognitive impairment with dysarthria, dysfluency, and expressive language deficits that are more severe than receptive language deficits. In most patients, the cerebrospinal fluid (CSF) to blood glucose ratio is below 0.50, and CSF lactate is low to normal.

This diagnosis can be confirmed by mutation analysis of the SLC2A1 gene, with analysis of glucose uptake into erythrocytes applied to confirm deficient GLUT1 function. Early diagnosis is critical because it allows for treatment with a ketogenic diet (high fat low carbohydrate diet that mimics the metabolic state of fasting) to reduce the frequency of seizures and dystonic movements. Since ketone bodies use another transporter to enter the central nervous system, they can supply an alternative source of fuel to the brain, effectively correcting brain energy metabolism [9,10]. The normal cerebral metabolic rate is low during the fetal and perinatal period, subsequently increasing in a linear fashion to peak at age 3 years and remaining high throughout childhood (followed by a gradual decline during adolescence). Therefore, childhood is the critical period for treatment with a ketogenic diet. Early diagnosis can allow for effective treatment with a ketogenic diet, which reduces the frequency of seizures and the severity of the movement disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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