


Abnormal gait and hypoglycorrachia in a toddler with seizures

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ABSTRACT

Introduction: Glucose transporter type 1 (Glut1) deficiency syndrome is a treatable neurometabolic disorder characterized by seizures, developmental delay, and hypoglycorrachia. Due to the rareness and non-specific clinical manifestations, it is usually mis- or underdiagnosed.

Case presentation: We report the case of a toddler who presented with afebrile epileptic seizures and abnormal gait. Brain imaging and electroencephalogram were normal. Further investigation of the cerebrospinal fluid revealed hypoglycorrachia that was the clue to the diagnosis of Glut1 deficiency syndrome and the initiation of treatment with ketogenic diet.

Conclusion: Our case highlights the importance of lumbar puncture while investigating a child with epileptic seizures and abnormal gait or developmental delay, in order not to miss treatable neurometabolic conditions, such as Glut1 deficiency syndrome.

KEYWORDS

Epilepsy, Glut1 deficiency, Developmental delay, Ataxia, Hypoglycorrachia

INTRODUCTION

Performance of lumbar puncture is not routinely incorporated in the evaluation of the first episode of afebrile seizures in children. However, the evaluation of cerebrospinal fluid (CSF) can often guide diagnosis to treatable conditions early in the course of the disease. Low glucose level in the CSF, or hypoglycorrachia, is defined as CSF glucose < 40 mg/dl and/or a CSF/serum glucose ratio ≤ 0.5 . Hypoglycorrachia may occur due to glycolysis by bacteria or impaired CSF glucose transport through the blood-brain barrier.¹ It is mostly attributed to central nervous system (CNS) infections, but also other causes such as carcinomatous meningitis, Glucose transporter type 1 (Glut1) defi-

ciency syndrome, leukemia/lymphoma with CNS involvement, and subarachnoid hemorrhage.^{1,2}

Glut1 deficiency syndrome is a rare treatable neurometabolic disorder affecting the CNS and caused by, mostly, *de novo* mutations of the glucose transporter gene *SLC2A1*.³ *SLC2A1* gene encodes a major glucose transporter (Glut1) which is primarily located in the blood-brain carrier.³ *SLC2A1* mutations abrogate the function of the Glut1 protein and lead to inadequate glucose levels and impaired cellular energy in CNS, with subsequent abnormal brain development and function.³ Laboratory investigations and brain imaging are usually normal, whereas neurophysiologic findings are non-specific and highly variable

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over time in children with Glut1 deficiency syndrome, and therefore do not contribute to the diagnosis.⁴ Hypoglycorrachia however is pathognomonic. In the present report, we describe the case of a boy presenting with non-specific afebrile epileptic seizures, gait abnormalities, and developmental delay, in which hypoglycorrachia was the clue to the diagnosis of Glut1 deficiency syndrome.

CASE REPORT

A 2-year-old boy was referred due to an episode of generalized tonic-clonic seizures. The child was reported to be at the nursery when he suddenly experienced loss of consciousness, eye deviation, and jerking movements of upper and lower limbs. The episode lasted less than 5 min, followed by postictal state. There was no report of fever, trauma, or other symptoms. He is the first child of non-consanguineous parents, delivered at term, after an uneventful pregnancy. Perinatal and past medical records were unremarkable apart from history of mild gross motor developmental delay. Specifically, independent walking has been achieved since the age of 19 months but he still experiences balance and gait difficulties. Family history was unremarkable.

Physical examination and vital signs upon arrival were normal. Postictally, he was slightly disoriented. Nuchal rigidity or other focal neurological signs were absent. Within 24 h of the convulsive episode, the toddler developed acute ataxic gait characterized by a wide-based and unsteady gait with features of spasticity (leg stiffness) without dystonia/chorea that resulted in three episodes of loss of balance and falls to the floor. The rest of the neurological examination, cranial nerve examination, cerebellar testing, and muscle strength/tone were normal. Complete blood count, arterial blood gases, renal and liver function tests were all within normal limits. CSF analysis was normal apart from low glucose (38 mg/dl, CSF/blood glucose ratio 0.45). CSF culture was sterile. Fundoscopy was normal. Brain computed tomography did not show any abnormality. Subsequent evaluation with brain magnetic resonance imaging revealed high-intensity areas at the deep white matter by the lateral ventricles, that were normal for the patient's age and were not associated with white matter volume loss (Figure 1). Electroencephalography showed normal activity and regular sleep organization without epileptiform changes. In the following days the patient improved gradually and gait instability subsided without any treatment. The finding of low CSF glucose in this episode was initially underestimated, as due to the rareness of the disorder, Glut1 deficiency was not initially considered.

However, on follow-up examination, one-month post-discharge, the parents reported occasional episodes of gait instability and loss of balance. The developmental evaluation demonstrated a global delay, with greater impair-

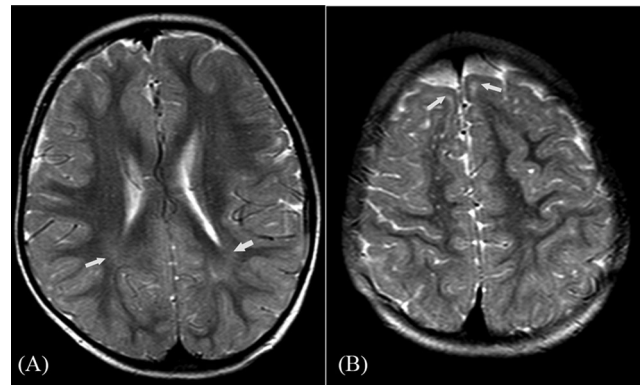


FIGURE 1 Magnetic resonance imaging (MRI) of the brain, T2-weighted sequence, the axial plane at the lateral ventricles, (A) and the convexity (B). There are high-intensity areas at the deep white matter by the lateral ventricles, clearly separated by the ventricular borders, without evidence of white matter volume loss (arrows in A) and at the subcortical U-fibers at the frontal lobes (arrows in B).

ment in verbal and motor skills. Parents were advised to seek occupational and speech therapy. Additionally, eight months later, the toddler experienced his second episode of afebrile generalized tonic-clonic convulsions of short duration. Diazepam was administered rectally and the episode resolved. Inadequate head control and gait instability were reported before and after the episode. Laboratory workup and fundoscopy upon admission were normal.

Due to the history of global developmental delay combined with afebrile convulsions and gait instability, further investigations were conducted. Laboratory investigation for inborn errors of metabolism was within normal limits. Lumbar puncture was repeated, and CSF analysis revealed normal lactate, amino acids, and neurotransmitters. Notably, biochemical analysis of CSF revealed repeatedly low glucose (39 mg/dl) and reduced CSF-to-plasma glucose ratio (0.44).

The hypoglycorrachia in this case in conjunction with developmental delay, epileptic seizures, and progressive gait abnormalities lead us to consider Glut1 deficiency syndrome. Indeed, sequencing of the glucose transporter gene, *SLC2A1*, revealed a novel heterozygous out-of-frame mutation (c.258_261del). *In silico* analysis (performed by Mutation Taster, based on the American College of Medical Genetics and Genomics guidelines) revealed that his alteration is pathogenic (disease-causing) as it causes a premature termination codon, leading to nonsense-mediated messenger RNA decay.⁵ Treatment with ketogenic diet was commenced, and resulted in clinical improvement and complete seizure control.

DISCUSSION

Glut1 deficiency syndrome is a severe neurometabolic disease that may be underdiagnosed as it presents with a

wide spectrum of non-specific signs and symptoms, and it may also appear with a milder phenotype without epileptic seizures. In this report, we present a boy with Glut1 deficiency syndrome that presented after infancy with seizures and gait instability. The recurrence of seizures together with the failure of the child to reach the developmental milestones lead us to further investigate the patient for neurometabolic disorders and perform a lumbar puncture. Low CSF glucose was the only abnormal laboratory result that guided us to a targeted genetic analysis for Glut1 deficiency syndrome.

Glut1 deficiency syndrome was first described in two patients in 1991, that presented with infantile-onset epileptic encephalopathy, developmental delay, acquired microcephaly, ataxia, and spasticity.⁶ Since then, approximately 500 cases have been reported, although many patients may be underdiagnosed as the disease includes a broad spectrum of neurological signs and symptoms. Most affected individuals with Glut1 deficiency syndrome present with drug-resistant epilepsy in the first months of life, developmental delay or intellectual disability, spasticity, hypotonia, acquired microcephaly, and a variety of movement disorders, such as choreoathetosis, dystonia, and ataxia.⁷ A mild phenotype, characterized by the presence of movement disorders and developmental delay without epileptic seizures, is seen in about 10% of individuals.⁸ The severity of symptoms vary significantly and correlate with the age of onset; epileptic seizures are mostly apparent in childhood whereas movement disorders are usually prominent in adults. The ketogenic diet, a high-fat carbohydrate-restricted diet that raises ketone levels through fat catabolism aiming to provide an alternative fuel for brain metabolism, is currently the recommended treatment for Glut1 deficiency syndrome and should be started as early as possible to provide adequate energy for brain development. Complete seizure control or at least seizure reduction is achieved in most patients when a ketogenic diet is initiated. Movement disorders are also often positively affected by the ketogenic diet although effects on developmental delay may vary and appear less prominent.⁹ Prognosis differs among affected individuals. Epileptic seizures typically decrease or even disappear in adolescence, whereas movement disorders either appear or worsen in adulthood. Intellectual disability remains stable throughout life.¹⁰

Given its rareness and its diagnostic challenges, it is of great importance to raise the clinical suspicion of the syndrome's clinical manifestations so that patients are early diagnosed and treated. Treatment should be initiated as soon as possible in order to achieve seizure control and prevent further disease progression. Low CSF glucose should not surpass unnoticed as it is often the clue to the diagnosis. In a child with seizures, developmental delay, or movement disorder, a lumbar puncture should be per-

formed, and in case of hypoglycorrhachia Glut1 deficiency syndrome should be suspected.

CONSENT FOR PUBLICATION

Consent has been given from the patient's parents.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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