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CLINICAL CASE

Phenotypic variability of GLUT1 deficiency: when is necessary to suspect?

Variabilidad fenotípica del déficit de GLUT1: ¿cuándo es necesario sospechar?

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What do we know about the subject matter of this study?

This pathology comprises a variable clinical combination of early-onset and refractory epilepsy (typically generalized, including absence seizures), cognitive impairment (from attention deficits to severe cognitive impairment), and movement disorders (from paroxysmal dystonia or chorea to persistent and severe ataxia and spasticity). Its diagnosis and treatment are highly specific, and clinical suspicion is essential.

What does this study contribute to what is already known?

This case of two half-brothers emphasizes that we should suspect this condition after an absence crisis before the age of 4 and even more so if there is a paroxysmal movement disorder. Although this is not the usual case, it also shows that there are cases of autosomal dominant inheritance. Based on these cases we provide an updated review of the subject.

Abstract

Glucose Transporter Type 1 Deficiency Syndrome (GLUT1-DS) is caused by the SLC2A1 gene mutation, which encodes the glucose transporter proteins to the brain Neurological manifestations occur in three main domains: seizures, abnormal movements, and cognitive disorders. The diagnosis is presumed upon the finding of low CSF glucose and confirmed by the gene molecular analysis. Accurate diagnosis is important because it has a specific treatment, which is ketogenic diet. **Objective:** To analyze two SD-GLUT1 pediatric patients with unusual phenotype. **Clinical Case:** We present the case of two siblings who presented absence seizures and a paroxysmal movement disorder. Both patients were studied, finding low CSF glucose. The diagnosis of GLUT1-DS was confirmed with molecular analysis. Specific treatment with ketogenic diet achieved good response in both cases. **Conclusions:** We present their peculiar clinical characteristics that allowed us to suspect this wide phenotypic spectrum. Correct and timely diagnosis and treatment can significantly improve the quality of life of those affected.

Keywords:
Glucose transporter;
Refractory epilepsy;
Abnormal movements;
Intellectual disability;
Ketogenic diet

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Introduction

Glucose is the main source of energy for the general nervous system and specifically for the brain. Its passage across the blood-brain barrier (BBB) dependent on the glucose transporter protein GLUT1[1]. This membrane protein is encoded by the SLC2A1 gene, which causes SD-GLUT1 mutations[2].

In 1999, De Vivo described this condition for the first time and reported two patients with difficult-to-treat seizures during the infant period and developmental delay, associated with persistent hypoglycorrhachia which suggests glucose transport failure to the BBB. Since this initial description, the phenotype has been expanded, reporting different clinical manifestations with varying severity[3].

The general objective of this article is to report an atypical presentation of SD-GLUT1, considering that it is a condition with a variable phenotype. We present two cases with relatively mild symptomatology which, if we do not know the possible variations of the disease, could go unnoticed.

Clinical Case

Case 1

Female patient, first child of healthy non-blood related parents, without a known relevant medical history. From the age of 3, she presents paroxysmal events while awake, characterized by altered state of consciousness and staring, of 30-seconds duration approximately, with a progressive frequency, presenting up to 15 episodes per day.

She was evaluated by a pediatric neurologist at the age of 4, presenting normal neurological examination and psychomotor development. The electroencephalogram showed normal base activity, with interictal epileptiform paroxysmal dischargers of spike-wave type. Brain MRI was normal. She was diagnosed with absence seizures and received treatment with valproic acid showing good response, with no new events for 2 years. At age 6, after six months of stopping treatment with antiepileptic drugs, the patient presented episodes of lower limb psychomotor agitation associated with pain and discomfort, preventing standing. The events occurred while awake, without altered state of consciousness, with duration about 1 minute and a frequency of 1 to 2 per month, without a clear trigger, although many of these events occurred before sleep. A restless leg syndrome was first considered but then ruled out.

After 4 years without epileptic seizures, she presented again absence seizures, therefore, treatment with valproic acid was restarted and later clobazam was added due to lack of response. In addition, we were able to use home video to identify the abnormal leg movements, which were classified as paroxysmal chorea. Neurological examination and school performance remained normal.

Case 2

Male patient, younger half-brother by mother side of Case 1. At age 3, he was evaluated due to atonic seizure (also called drop seizure, akinetic seizure or drop attack) with apparent muscle tone and strength loss of lower extremities and without altered state of consciousness. The episodes lasted around 5 minutes, occurring once or twice per month, with unidentified triggers. Hyperkalemic periodic paralysis was suspected and then ruled out.

The patient presented typical absence seizures at the age of 4, with similar electroencephalogram results to that of Case 1. Seizures persisted after treated with valproic acid. The neurological examination was normal, except for slight hyperactivity and impulsivity. Therefore, an autosomal-dominant SD-GLUT1 was suspected.

The cerebrospinal fluid (CSF) study of both siblings showed hypoglycorrhachia (Case 1: glycorrhachia 33mg/dl, glycorrhachia/glycemia ratio 0.39; Case 2: glycorrhachia 31mg/dl, glycorrhachia/glycemia ratio 0.55, normal value CSF/serum glucose ratio > 0.4).

The diagnosis was confirmed with a sequencing study of the SLC2A1 gene in Case 1, which showed a heterozygous point mutation (c.694C > T - p.Arg32Cys). Both siblings were put on the ketogenic diet. They continued with antiepileptic treatment, without modification, achieving remission of epileptic seizures and dyskinesia of lower limb within 2 months of onset. To date, they remain asymptomatic with a follow-up of 18 months. Regarding cognitive status, there were no major clinical changes after started the ketogenic diet, however, psychometric assessments were not available.

Discussion

The brain is the most energy-consuming organ, but it has little capacity to store energy as glycogen, requiring a continuous supply of glucose or, failing that, alternative fuel such as ketone bodies[3]. GLUT1 is a membrane-bound glycoprotein expressed in erythrocytes, brain capillary endothelium and astrocytes[4], which allows the passage of glucose across the BBB.

SLC2A1 is the gene encoding GLUT1, it is located on chromosome 1 (1p34.2), is 35 kb in size and consists of 10 exons[5]. Several mutations in this gene (about 100 described to date), produce a loss of function, in other words, reduce the supply of glucose to the bra-

in, resulting in energy deficiency that damage brain function and neurodevelopment[3].

It has been described that 84% of genetic mutations correspond to specific ones and 13% to deletions/duplications[2]. Animal models, electrophysiological and functional neuroimaging studies with marked glucose have proved that mutations in the SLC2A1 gene produce dysfunction in thalamic-cortical connectivity, which determines the frequency of finding 3 Hz interictal epileptiform dischargers of spike-wave type and relative glucose overload in the basal nuclei, which could be related to movement disorders[6].

Most patients present *de novo* heterozygous mutations. Familial forms are generally autosomal dominant[3]. Biallelic mutations in the SLC2A1 gene would be lethal in most cases, although cases with autosomal recessive transmission have been reported[7,8]. There is no definite genotype-phenotype correlation, and there is high phenotypic variability, even within the same family. Other genetic, epigenetic or environmental factors may influence the phenotype, as well as the presence of alternative sources such as endogenous ketone bodies as substrates for the brain[3].

The SD-GLUT1 mutation presents a wide severity spectrum, ranging from patients with minimal symptoms and no clinical signs between episodes to patients with severe and fixed neurological deficits. This condition presents neurological manifestations, mainly the following three symptoms: epileptic seizures, movement disorders, and cognitive-behavioral impairment.

The phenotype of the classic SD-GLUT1 mutation is characterized by persistent symptoms in all 3 domains. In contrast, patients with milder phenotypes may have symptoms in only 1 or 2 domains and may present intermittently or persistently[9]. The classic phenotype is characterized by drug-resistant epilepsy which onset usually occurs in the first months of life, global developmental delay, acquired microcephaly, spasticity, ataxia, and abnormal movements[3,5].

Seizures usually occur in the infant period and are refractory to antiepileptic drugs[10,11]. There are several types of epileptic seizures, where the most frequent are the generalized tonic-clonic ones and the absence ones[12]. Table 1 shows some signs that, in the face of absence crises, should make us suspect the diagnosis of SD-GLUT1 mutation.

We can commonly observe movement disorders. Patients present a range of persistent and/or paroxysmal motor symptoms[9], most of them are ataxic gait with or without spasticity, dystonia, chorea, intention tremor, dyspraxia, and myoclonus.

Common triggers of episodic symptoms are fasting and exercise, although sometimes no trigger can be identified, as in the cases reported in this article. Among the paroxysmal events presented in SD-GLUT1, we highlight exercise-induced paroxysmal dyskinesia which characteristics are episodes of different involuntary movements, usually lasting 5 to 30 minutes, triggered by continuous exercise and usually appear during childhood. Lower limb dystonia due to continuous walking or running is the most common manifestation, but myoclonus, athetosis, chorea, and ballismus can also occur, isolated or combined[9].

The high rate of clinical suspicion and the greater availability of genetic studies have allowed broadening the clinical spectrum, detecting patients without epileptic seizures who may have movement disorders as the most prominent feature[9].

Most patients experience some degree of cognitive impairment, ranging from mild learning disabilities to severe intellectual disabilities. However, it is important to note that there are patients with normal cognitive development[9]. In SD-GLUT1 carriers, sustained attention appears to be a particularly affected function[9]. Also, there are rare extraneurological signs such as hemolytic anemia (considering that GLUT1 is the main glucose transporter in red blood cells), hepatosplenomegaly, and cataracts[3,9].

Following clinical suspicion, diagnostic confirmation is based on CSF cytochemical study, which shows hypoglycorrhachia, and on the molecular study of the SLC2A1 gene, which evidences some pathogenic mutation. To determine hypoglycorrhachia, it is necessary to analyze CSF after four to six hours of fasting and present normal concomitant glycemia levels.

To date, all the individuals reported have had CSF glucose values < 60 mg/dL (range 16.2 to 52 mg/dL), and over 90% of cases presented < 40 mg/dL, which is considered highly suggestive of SD-GLUT1 mutation. Also, values between 40 and 60 could be relevant.

Table 1. Characteristics of absence seizures that lead to suspicion of GLUT1-SD

- Early onset < 4y
- Appearance early in the morning or after fasting
- Drug resistant
- Early association with other seizure (myoclonus, tonic-clonic and less frequently focal or tonic)
- EEG with short and frequent interictal activity
- Irregular form and frequency of generalized discharges
- History of other types of neurological manifestations (hypotonia, microcephaly, ataxia, migraine, instability, paroxysmal involuntary movements)
- Cognitive and attentional difficulties may emerge later

Another value to analyze is the CSF glucose/blood glucose ratio, which is usually < 0.4. Such value is less reliable than the absolute value of CSF glucose. CSF lactate concentration is normal-low or low, which is frequently < 11.7 mg/dl (range 5.4 to 13.5 mg/dl)[2,13].

SLC2A1 is the only gene so far known that causes SD-GLUT1 mutation. Therefore, it is recommended to perform the sequence analysis first and, if no pathogenic variant is identified, to practice the deletion/duplication analysis[2].

Currently, the ketogenic diet is the mainstay of treatment[3], which was effective in both cases regarding seizures and movement disorder control. The use of the ketogenic diet is based on the fact that when glucose supply is insufficient, endogenous ketone bodies are the only relevant alternative source of fuel for brain metabolism[3]. Due to the high energy demand during brain development, the ketogenic diet should start as early as possible and maintained at least until adolescence, although it also appears as beneficial even when it started in late childhood. If there is low adherence during adolescence, we would change to the modified Atkins ketogenic diet, which is less restrictive. Typical outcomes of the ketogenic diet include complete remission, or at least reduction, of seizures, quick disappearance of non-epileptic paroxysmal disorders, slow reduction of persistent movement disorders, but little improvement regarding neurodevelopmental and cognitive functions[3].

We can also use medications to manage residual symptoms, however, they are usually not very effective[12,14]. Acetazolamide may be the first choice for treating paroxysmal movement disorders[15,16]. Drugs that potentially alter GLUT1 function should be avoided, including caffeine, phenobarbital, diazepam, valproate, and tricyclic antidepressants[14,17]. Appropriate rehabilitation, including physical, speech and occupational therapy, is essential, along with promoting school and professional inclusion[3].

Conclusions

The SD-GLUT1 mutation is a rare disease, but with a growing number of cases diagnosed in recent years, which has allowed the recognition of a wide phenotypic variability. This article describes two patients with early-onset epilepsy, with good initial response to antiepileptic drugs, who subsequently presented abnormal movements, without clinical evidence of cognitive impairment. Although hyperactivity and impulsivity are described in Case 2, it is not possible to determine whether this is due to SD-GLUT1-related symptoms or a highly prevalent attention-deficit/hyperactivity disorder in the population. Both cases showed an excellent response to treatment with the ketogenic diet. Knowledge and a high diagnostic suspicion index allow the diagnosis of patients with variable phenotypes. Currently, the available molecular genetic studies allow achieving the definitive diagnosis. The implementation of specific and effective treatment allows improving the quality of life of the patients.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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