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CLINICAL CASE

Glucose Transporter Deficiency Syndrome (GLUT-1): Case Report and Novel Pathogenic Variant of the SLC2A1 Gene

Síndrome de deficiencia del transportador de glucosa cerebral (GLUT-1): Reporte de caso y variante patogénica nueva del gen SLC2A1

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

GLUT1-DS is a metabolic disease caused by a defect in the glucose transport to the brain. The phenotypes are variable. Most cases are caused by de novo mutations of the SLC2A1 gene. The ketogenic diet is the treatment of choice.

What does this study contribute to what is already known?

We report the case of a patient with a classic GLUT1-DS phenotype carrying the c.1300T>A (p.Phe434Ile) mutation in the SLC2A1 gene, previously reported as a variant of uncertain significance, but which we consider pathogenic and responsible for this disease based on the clinical presentation, conservation analysis, and bioinformatic studies. This case emphasizes the importance of CSF analysis and molecular studies in patients with certain epilepsy phenotypes and/or neurodevelopmental delays.

Abstract

Glucose transporter 1 deficiency syndrome (GLUT-1 DS) is caused by mutations in the *SLC2A1* gene in most patients, resulting in impaired glucose transport to the brain. A variety of phenotypes may present, including epilepsy, intellectual disability, and movement disorders. **Objective:** To report a case of GLUT-1 DS associated with a new variant of the *SLC2A1* gene. **Clinical Case:** A six-year-old female patient diagnosed with refractory epilepsy at the age of two. Pharmacological management was initiated when she was four years old. Microcephaly and delayed neurodevelopment were observed. She was admitted due to an exacerbation of seizures. A genetic panel revealed

Keywords:
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a variant in the *SLC2A1* gene (A>T), which replaces the amino acid phenylalanine at codon 434 with isoleucine (p.Phe434Ile). This variant has not been previously described in the medical literature but is likely pathogenic. Biochemical analysis of cerebrospinal fluid glucose showed hypoglycorrhachia, confirming the diagnosis. A ketogenic diet was initiated, leading to a marked reduction in seizures. **Conclusions:** GLUT-1 DS is a rare neurometabolic disease, in which timely diagnosis is essential to initiate the primary treatment with a ketogenic diet. This approach has been demonstrated to be the treatment of choice for seizure control and may also have a positive impact on cognitive and motor function. The presented case features a variant in the *SLC2A1* gene that can be considered pathogenic.

Introduction

GLUT1 deficiency syndrome (GLUT1-DS) was first described in 1991. It was initially described as an early-onset epileptic encephalopathy[1]. However, over time a much broader clinical picture has been demonstrated, with varied manifestations and even adult presentations. It is caused by an alteration in glucose transport across the blood-brain barrier. The alteration of the facilitated glucose transporter GLUT1 results in low glucose levels in the cerebrospinal fluid (CSF), also known as hypoglycorrhachia[2].

Most patients carry mutations in the *SLC2A1* gene encoding the GLUT1 transporter[2]. Increasing numbers of cases are being reported due to the availability of molecular studies. A recent population-based study in Scotland reported an incidence of 1:24,000, considering patients with epilepsy onset before the age of three years[3].

The classic phenotype is characterized by early-onset epileptic encephalopathy (before the age of two) accompanied by movement disorders, paroxysmal events, microcephaly, and neurodevelopmental delay. The low glucose concentration in the CSF with normal blood glucose levels represents the biochemical hallmark of the disease. In the context of an increasing complexity of symptoms, mutations, and treatment regimens, the diagnosis and management of GLUT1-DS has become a challenge[3,4].

This increasing complexity led to the recent publication of a consensus for the diagnosis and treatment of GLUT1-DS[5]. The importance of timely diagnosis lies in the fact that management with a ketogenic diet has shown good seizure control, with a positive impact on prognosis and associated comorbidities. The objective of this report is to present a case of GLUT1-DS with refractory epilepsy, developmental delay, and microcephaly associated with a new variant of the *SLC2A1* gene.

Clinical Case

6-year-old female patient, born at term in Venezuela, residing in Medellin, Colombia. At 2 years of age, she started frequent epileptic seizures presenting two types of semiology: some with tonic posture and drowsiness lasting 1-2 minutes, sometimes followed by screaming and flashing light vision, and others with behavioral arrest and staring spells. She also presented with unsteady gait, microcephaly (-2 SD), and global neurodevelopmental delay, achieving independent walking at the age of two and beginning to speak at the age of three. She was evaluated by pediatric neurology at our institution at the age of 5. At the time of the assessment, she communicated using short phrases and showed expressive language impairment. At that time, she was being treated with Oxcarbazepine (45 mg/k/day), without achieving adequate seizure control. The EEG showed spontaneous generalized epileptiform activity with 3 Hz spike and slow wave complexes, and the brain MRI was normal.

Considering the clinical presentation, it was decided to further testing with a genetic epilepsy panel, which identified a heterozygous mutation in the *SLC2A1* gene, A > T variation, which replaces the amino acid phenylalanine at codon 434 with isoleucine (p.Phe434Ile). This variant had not been previously described in the medical literature and was classified as of uncertain significance but reported as likely pathogenic[6]. Heterozygous pathogenic variants in the *SLC2A1* gene are associated with GLUT1-DS.

Based on this genetic result, a CSF analysis was performed, which showed hypoglycorrhachia (21.6 mg/dl) and a CSF-to-blood glucose ratio of 0.44, confirming the clinical suspicion of GLUT1-DS. The variant was also considered a novel mutation not previously reported. Following this confirmation, a modified ketogenic diet was initiated, which showed marked clinical improvement and total epileptic seizure control.

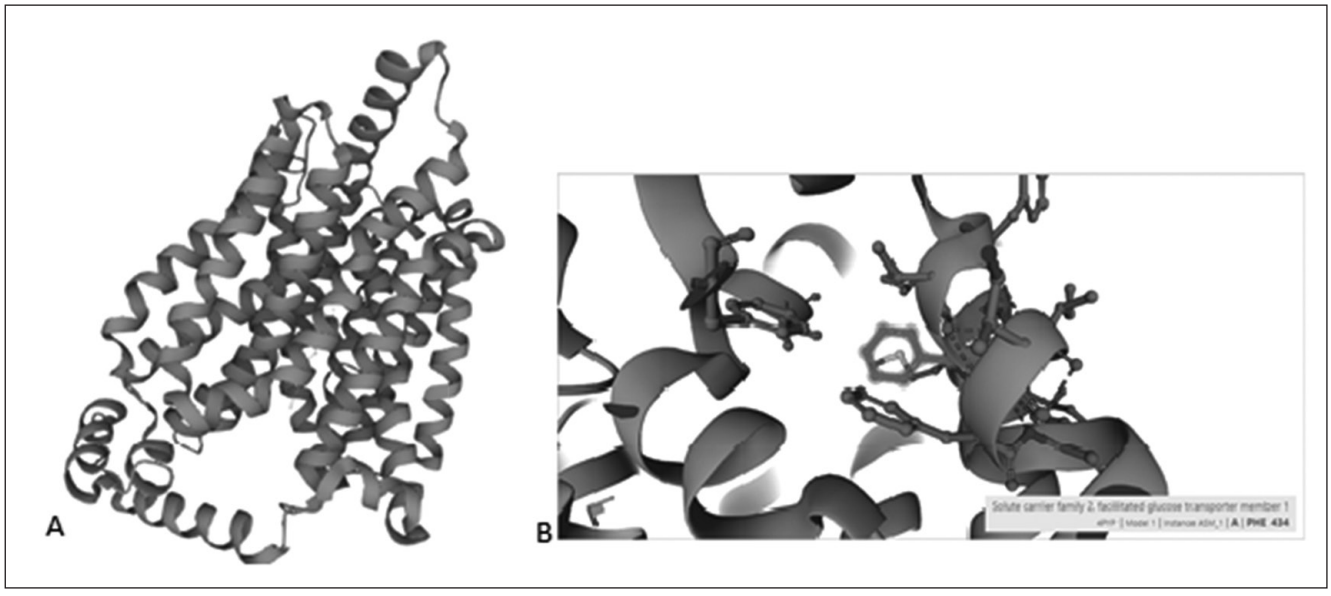

Figure 1. Three-dimensional structure of the protein using UniProtKB20. **A)** The protein is shown, and the location of the amino acid Phe at position 434 is highlighted in green. **B)** The phenylalanine at position 434 is shown with its possible interactions.

Table 1. Conservation analysis. Comparison of species with a mutant amino acid in membrane transporter proteins of the Solute Carrier (SLC) Family 2 Member 1. Adapted from MutationTaster[12]

species	aa	alignment
Human	434	Q Y V E Q L C G P Y V F I I F T V L L V L F F I
mutated	434	Q Y V E Q L C G P Y V **I** I I F T V L L V L F F
Ptroglodytes		
Mmulatta	434	Q Y V E Q L C G P Y V **F** I I F T V L L V L F F
Fcatus		
Mmusculus	434	Q Y V E Q L C G P Y V **F** I I F T V L L V L F F
Ggallus	432	I A Q L C G S Y V **F** I I F T V L L V L F F
Trubripes	468	Q Y L V E L C G P Y V **F** I I F T V L L L L F F
Drerio	434	E E V C G A Y V **F** V I F T V F L L C F F
Dmelanogaster	740	P S M K T A L E N Y T **F** L P F S V F L A I F W
Celegans	473	L P I N N L M Q Q Y S **F** F I F S G F L A F F I
Xtropicalis		

Discussion

GLUT1-DS is an inborn error of metabolism with specific treatment. The diagnosis is based on clinical symptoms and confirmed by CSF findings and pathogenic variants of the *SLC2A1* gene[7,8]. Our patient presented a compatible clinical and biochemical picture and a mutation that had not been reported in the literature until now.

There are two described phenotypes of GLUT1-DS: classic and non-classic. The classic phenotype (90%) is characterized by seizures that usually start before the

age of two, acquired microcephaly, psychomotor developmental delay or intellectual disability, and movement disorders ranging from paroxysmal eye disorders, ataxia, dystonia, or chorea. In the non-classical phenotype (10%), there are usually no seizures, and they have dyskinesias or movement disorders such as intermittent ataxia, choreoathetosis, dystonia, or alternating hemiplegia[2,9].

The reported case is consistent with the classic phenotype, with early absence seizures and focal seizures, in this case with onset in the upper range of those described in the literature (2 years), but also described in other case series[8,9]. Additionally, the patient had microcephaly, neurodevelopmental delay, and ataxic gait.

The GLUT1 protein is encoded by the *SLC2A1* gene (1p34.2). Most cases of GLUT1-DS are caused by pathogenic or probably pathogenic heterozygous mutations in this gene. They are usually *de novo* mutations with complete penetrance. The encoded protein consists of 492 amino acids and is found mainly on the cell surface; it has a ubiquitous distribution, is highly expressed in the brain and erythrocytes, and is primarily responsible for cellular glucose uptake[10]. The clinical manifestations result from brain energy failure due to the inability to use glucose[9], the brain's primary fuel.

In the reported case, genetic testing was performed which showed a point mutation in the *SLC2A1* gene, in which the amino acid phenylalanine at codon 434 is replaced by isoleucine (p.Phe434Ile), of uncertain significance/probably pathogenic. Phenylalanine at position 434 (Figure 1) is important for the formation of a helix. The c.1300T > A (p.Phe434Ile) mutation of the *SLC2A1* gene had not been reported previously in the literature in The Human Gene Mutation Database or ClinVar[11,12]. This missense mutation has a phyloP100 conservation score of 9.18, conserved in most species (Table 1).

Most bioinformatics programs mention that this variant is pathogenic (Mutationtester, Provean, Polyphen2), and assessment in Varsome[6] classifies it as probably pathogenic since it complies with PP3 (Pathogenic Supporting-in silico pathogenicity predictions), PM5 (Pathogenic Moderate-new change in an amino acid where a different change is already considered pathogenic), PM2 (Pathogenic Moderate-low frequency or absence in controls), and PP2 (Pathogenic Supporting-missense in a gene where there are few missenses in controls and where such variants cause disease) according to the recommendations of the American College of Medical Genetics (ACMG)[13].

The c.1300T > G (p. Phe434Val) rs1570590528 mutation in the *SLC2A1* gene has been previously reported as probably pathogenic and associated with GLUT1-DS type 2 (OMIM #612126), which confirms that the alteration in this amino acid can cause an alteration in the protein.

The patient described in this report had a typical clinical picture and, given the finding in the genetic study, a biochemical profile was performed, showing hypoglycorrhachia (CSF glucose levels < 40 mg/dl; CSF/blood glucose ratio < 0.45) confirming the diagnosis of GLUT1-DS, which supports the pathogenicity of the mutation found.

Lumbar puncture is not routinely incorporated in the evaluation of the first episode of afebrile seizures in children. However, CSF evaluation can sometimes guide the diagnosis of treatable conditions early in the course of the disease, which impacts prognosis[14]. Patients with GLUT1-DS typically have epilepsy or movement disorders as the primary diagnosis. The diagnostic possibility of GLUT1-DS should be explored in patients with some combination of the following clinical features including early-onset drug-resistant epilepsy, acquired microcephaly, movement and gait disorders (ataxia, dystonia, chorea, spasticity without clear cause), and paroxysmal abnormal movements such as oculocephalic ones since they are highly suggestive, but also other paroxysmal movements/dyskinesias, with or without intellectual disability[9,15,16]. It is also suggested to study early onset absence epilepsy (before 4 years of age) and epilepsy with myoclonic-atonic seizures or Doose syndrome[5].

When GLUT1-DS is suspected, the best course of action is to perform a CSF analysis via lumbar puncture after a 4- to 6-hour fast, along with obtaining a simultaneous central blood glucose measurement. A CSF result suggestive of GLUT1-DS consists of hypoglycorrhachia (< 40 mg/dl; range 16.2-52 mg/dl) and CSF/blood glucose ratio < 0.4 (range 0.19-0.59), in the context of normal blood glucose and CSF lactate levels, in order to rule out other causes of hypoglycorrhachia[2,9]. The next step is the molecular analysis of the *SLC2A1* gene, which can be performed through sequencing, though it is more commonly done currently using genetic panels or targeted epilepsy exome analysis by next-generation sequencing (NGS).

Timely diagnosis is essential to provide targeted treatment, which in this case is a ketogenic diet, which provides ketones as an alternative fuel for the brain[17,18]. The ketogenic diet is the management of choice in GLUT1-DS. It mimics a fasting metabolic state which maintains ketosis by replacing carbohydrates and proteins with fats in different proportions. In the setting of hypoglycorrhachia, ketones serve as an alternative fuel for the brain and effectively reverse the cerebral "energy crisis".

Epileptic seizures usually improve significantly in most patients managed with a ketogenic diet, as well as gait disorders and partial movement and cognitive

Table 2. Comparison of indications and treatment recommendations with ketogenic diet in drug-resistant childhood epilepsy and Glut-1 DS. Adapted from Keppler, 2020[5].

Criteria	Ketogenic diet for drug-resistant childhood epilepsy	Ketogenic diet for Glut1 deficiency syndrome
Indication: Epilepsy Movement disorder Developmental disorder	Poor seizure control with ≥ two antiseizure medications	First line treatment.
Treatment: Start	Optional	At the time of diagnosis, at any age, as early as possible
Duration	2 years/+	Adulthood (there is no clear "end date," but its benefits are thought to extend over time)
Ketosis and ketogenic diet ratio	Variable	As high as tolerated
Low glycemic index treatment (LGIT)	Optional	Not recommended
Ketosis monitoring	Blood and urine ketones	Blood ketones
Carnitine levels	Optional	Recommended
Side effect monitoring	(+)	(+++)

function disorders[5,17]. A 2019 publication[18] describing the response to the ketogenic diet in 270 patients with GLUT1-DS (case reports and case series) found that epilepsy improved in 83% and remained unchanged in 17%, movement disorders improved in 82% and remained unchanged in 17%, and cognitive function improved in 59% and remained unchanged in 40% of patients.

The management of the ketogenic diet in GLUT1-DS does not differ substantially from the diet used for the treatment of other types of epilepsy. However, the consensus published in 2020 provides specific recommendations to consider in the initiation and follow-up of these patients[5] such as starting as early as possible in the course of the disease, measuring ketonemia periodically, and the types of ketogenic diet to be used (Table 2). The classic ketogenic diet produces a higher degree of ketosis and is the preferred diet in children under three years of age. However, there is another type of ketogenic diet that can be used in older children and adolescents such as the modified Atkins diet, which may be better tolerated as it is less strict. This type of diet has also been used in GLUT1-DS with reports of improvement[18]. However, the higher the ketogenic rate and the younger the age of initiation of the diet, the greater the effectiveness[19].

Conclusions

GLUT1-DS is a neurometabolic entity with a specific treatment, presenting with a broad phenotypic spectrum. Diagnosis is based on a set of clinical manifestations accompanied by hypoglycorrhachia and confirmation with characteristic genetic variants. The c.1300T>A (p.Phe434Ile) mutation in the *SLC2A1* gene is considered to be the cause of this disease (pathogenic) based on the patient's clinical manifestations, conservation analysis, and bioinformatic studies. The importance of early diagnosis lies in the fact that treatment with a ketogenic diet has an important impact on seizure control and probably contributes to the improvement of motor and cognitive function.

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.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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