Glucose Transporter Type 1 (GLUT1) Deficiency Syndrome: A Case Report

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Abstract

The human brain represents only 2% of an adult individual's body weight. However, it requires 25% of the energy consumed by the body. This energy, primarily delivered to the brain in the form of the nutrient glucose, must cross the blood-brain barrier (BBB) through glucose transporter 1 (GLUT1), the main cerebral hexose transporter. Therefore, the levels of this transporter could affect brain function.

It is now recognized that Glut1 Deficiency Syndrome is significantly underreported. It follows an autosomal dominant inheritance pattern, with 90% of cases resulting from de novo mutations, while a small percentage are inherited in an autosomal recessive manner.

This report reviews the case of an adult patient with refractory epilepsy and progressive deterioration, whose clinical characteristics and genetic study confirmed the SLC2A1 mutation, establishing the diagnosis and highlighting the importance of considering this condition in differential diagnoses.

Keywords: Glut1; Glut1 deficiency syndrome; SDGLUT1; epilepsy; ketogenic.

Case Presentation

This is a 25-year-old male patient. Maternal obstetric history: 25-year-old mother, gravida 2, cesarean section 2, with the patient being the product of the first pregnancy. Parents are non-consanguineous. The patient was born at term (40 weeks) via elective cesarean section due to maternal hemorrhoids. Apgar scores were 9-9-10, with weight and length appropriate for gestational age, and no need for neonatal unit hospitalization.

Neurodevelopment appeared normal until 7 months of age, achieving head control, sitting, and initiation of crawling. Subsequently, he developed progressive developmental delay with regression of previously acquired milestones, including crawling. He has a history of multiple orthopedic surgeries due to bilateral congenital clubfoot and deformative dysplasia of the hip and spine. At age of 7, bilateral femoral osteosynthesis plates were placed. Additionally, he was diagnosed with hypothyroidism, possibly secondary to prolonged valproate use, and bone demineralization.

The first seizure occurred at 7 months of age, averaging 5 to 6 seizures daily. Currently, he presents with dystonia lasting approximately five minutes, with a frequency of one episode per day, without loss of consciousness and not triggered by external stimuli. From the onset of epilepsy, he was treated with magnesium valproate, and levetiracetam was added at age 7 due to persistent seizures. He has simultaneously received neurodevelopmental therapy. He was initially diagnosed with cerebral palsy and cerebellar hypoplasia syndrome, considered possibly syndromic due to associated malformations. His mother reports that at some point, molecular testing for Wilson's disease was performed, reported as positive, although karyotype was normal 46,XY, and penicillamine treatment was initiated.

Brain MRI (10/29/2018) revealed alterations in the posterior insular regions compatible with changes secondary to perinatal hypoxic-ischemic injury, along with reduced volume in the frontal topography. A collection in the posterior fossa communicating with the fourth ventricle was observed, associated with cerebellar vermis hypoplasia, a finding compatible with a Blake's pouch cyst.

At the age of 19, despite no new seizure episodes, he was evaluated by clinical genetics. The following studies were requested:

- High-resolution peripheral blood karyotype (normal result

- Plasma amino acid chromatography (within normal limits).
- Urine amino acid chromatography, showing bands migrating in the position of cystine, lysine-histidine-ornithine, and glycine-serine, without findings suggestive of an aminoacidopathy.

In the context of suspected Wilson's disease, a heterozygous variant c.4301C>T (p.Thr1434Met) was identified in the ATP7B gene, of uncertain clinical significance, since ceruloplasmin and serum copper levels were normal in 2018. Subsequent deletion/duplication analysis of the ATP7B gene was negative.

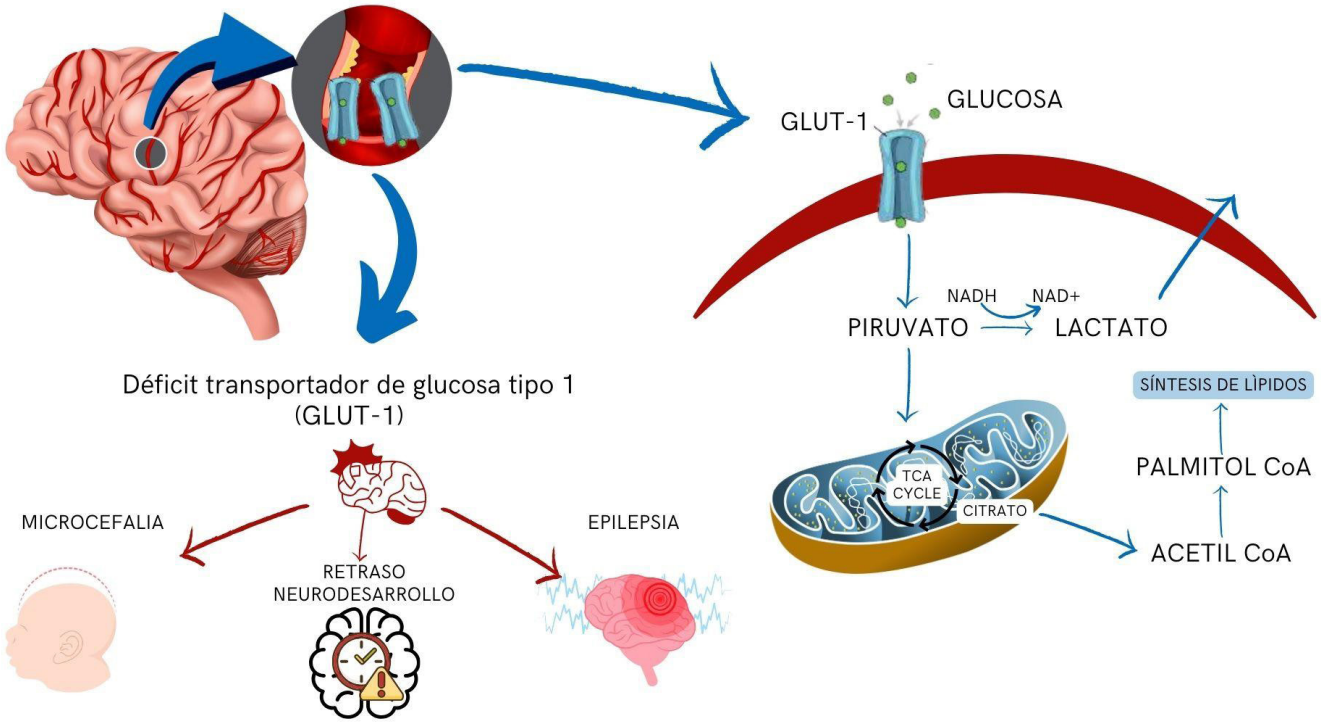
Additional metabolic screening (urinary carbohydrate tests with Benedict, Seliwanoff, and glucose oxidase, as well as serum pyruvic acid and ammonium) was requested but not authorized by the health insurance provider (EPS).

Finally, in order to establish the genetic etiology of the condition, trio exome sequencing was performed, which revealed a de novo heterozygous pathogenic variant c.972+1G>T in the SLC2A1 gene, located at a canonical splicing site (intron 7/9). This finding is consistent with a diagnosis of childhood-onset GLUT1 deficiency syndrome (GLUT1-DS) with autosomal dominant inheritance. The parents are not carriers of this mutation.

Discussion

Glucose transporter type 1 deficiency syndrome (GLUT1-DS) is a treatable epileptic encephalopathy caused by a defect in the GLUT1 protein, which is predominantly expressed in endothelial cells of the blood–brain barrier (BBB) and in astrocytes, while the GLUT3 transporter is mainly located in neurons (2). This syndrome was first described in 1991 (3). Thanks to current molecular diagnostic tools, its incidence has been estimated at approximately 1 per 240,000 live births with epilepsy of onset within the first three years of life. Retrospective studies have reported a prevalence of 1:83,000 in Denmark and 1:90,000 in Australia (4). GLUT1 deficiency results in a shortage of glucose in the brain, leading to an early-onset energy encephalopathy (2). See Figure 1.

Figure 1. Neurometabolic consequences of glucose transporter type 1 (GLUT1) deficiency: early-onset energy encephalopathy.



The alteration in glucose transport across the BBB and into astrocytes produces a "cerebral energy crisis" that manifests clinically with childhood-onset epilepsy—often drug-resistant—, impaired head growth, neurological developmental delay, and complex movement disorders, including paroxysmal head and eye movements (5).

The syndrome follows an autosomal dominant inheritance pattern (6). The SLC2A1 gene, located on chromosome 1p34.2, encodes the GLUT1 transporter, a glycoprotein consisting of 492 amino acids, organized into 10 exons and 9 introns. It has been observed that GLUT1 and GLUT3 concentrations are low at birth and progressively normalize by the weaning period, a critical stage of brain development and maturation (2). Approximately 90% of mutations are de novo, while a smaller percentage follows an autosomal recessive pattern. In the case presented, a heterozygous de novo c.972+1G>T variant in SLC2A1 was identified, with both parents negative for the mutation.

Genetic variability in this syndrome generates a broad phenotypic spectrum. Although some patients have initially normal development during the first months of life, seizures usually begin before six months of age. These

may include generalized, clonic, focal, myoclonic, and absence seizures, as well as episodes such as apnea and abnormal ocular movements resembling opsoclonus, which in some cases precede epileptic seizures (7,8). In the reported patient, seizures began at seven months of age, with features consistent with the literature.

Diagnosis should be suspected when there is a combination of suggestive clinical findings and biochemical evidence of hypoglycorrhachia (<60 mg/dL or <3.3 mmol/L) with normal or low cerebrospinal fluid lactate levels (<9 mg/dL or <0.5 mmol/L) (9,10). Confirmation is achieved through molecular analysis, identifying mutations in the SLC2A1 gene, which have been associated not only with the classic syndrome but also with other epileptic forms, such as early-onset absence seizures (10% of cases), genetic generalized epilepsies (1%), and myoclonic-astatic epilepsy (5%) (11). Molecular diagnosis also enables the reclassification of variants previously considered of uncertain significance and broadens the phenotypic and therapeutic understanding of the disease.

The treatment of choice is the ketogenic diet (12), a high-fat, low-carbohydrate regimen with an adequate amount of protein, which mimics the metabolic state of fasting. Under these conditions, the body generates ketone bodies—mainly beta-hydroxybutyrate and acetoacetate—that supply the brain's energy needs in the absence of glucose. The anticonvulsant mechanisms of the ketogenic diet include changes in cerebral metabolism, reduction of neuronal excitability, modulation of neurotransmitter transmission, and the action of circulating factors with neuromodulatory effects.

The use of antiepileptic drugs in the context of GLUT1 deficiency syndrome is controversial and generally discouraged. These therapies do not correct the underlying metabolic defect and, in addition to being ineffective in most cases, may induce significant adverse effects (2,13). The potential of lipoic acid has been studied, as it facilitates glucose transport in muscle cells via GLUT4. In vitro studies have demonstrated a similar effect on GLUT1, leading to its proposed use as a supplement in this condition. However, clinical evidence is limited, and the doses required to achieve effects comparable to experimental models are unattainable by oral administration, making its clinical benefit, at best, modest (14).

Recently, it has been suggested that ketones may have direct anticonvulsant effects, and polyunsaturated fatty acids could also play a role in

neuronal protection. Nonetheless, these hypotheses lack sufficient support from clinical trials (15). Current research is focused on developing biological therapies aimed at enhancing the expression and function of the GLUT1 transporter, although these remain in the experimental stage.

Conclusions

We report the case of a patient with glucose transporter type 1 deficiency syndrome (GLUT1-DS), whose clinical presentation was consistent with the literature and whose diagnosis was confirmed by genetic sequencing, identifying the heterozygous de novo pathogenic variant c.972+1G>T in the SLC2A1 gene.

This case highlights the importance of a comprehensive approach in patients with early-onset, drug-resistant epilepsy and neurodevelopmental delay, in whom this treatable neurometabolic syndrome should be considered as part of the differential diagnosis.

Although molecular analysis is essential for diagnostic confirmation, it is important to note that a proportion of patients with suggestive clinical features may not present identifiable SLC2A1 variants, underscoring the value of clinical diagnosis based on phenotype.

Therefore, a multidisciplinary approach—including neurology, genetics, internal medicine, nutrition, and rehabilitation—is emphasized to ensure comprehensive management aimed at improving quality of life and preventing the progression of associated complications.

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