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Glucose transporter type 1 deficiency syndrome: clinical aspects, diagnosis, and treatment

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ABSTRACT

Glucose transporter type 1 deficiency with a typical onset is a genetic disorder associated with the *SLC2A1* gene. Usually appears during the first years of life with severe developmental delay, drug-resistant epilepsy, and movement disorders. Diagnosis is suspected based on clinical manifestations and a low glucose level in cerebrospinal fluid, and should be confirmed by the molecular genetic study of the *SLC2A1* gene.

As it is a rare disease with variable clinical expression, early diagnosis is often challenging for the healthcare team. Nevertheless, this is important because early implementation of ketogenic therapy will lead to control of the clinical manifestations and a better long-term prognosis.

Here we review the glucose transporter type 1 deficiency syndrome focusing on its clinical, biochemical, molecular, and therapeutic characteristics.

Key words: *glucose transporter type 1,* SLC2A1*, dyskinesias, epilepsy, ketogenic diet.*

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LIST OF ABBREVIATIONS

CSF: cerebrospinal fluid
CNS: central nervous system
GLUT1: glucose transporter type 1
GLUT1DS: glucose transporter type 1 deficiency syndrome
KD: ketogenic diet
KDT: ketogenic diet therapy
MAD: modified Atkins diet

INTRODUCTION

Glucose transporter type 1 deficiency syndrome is a neurometabolic disorder that usually appears in the first months of life and is secondary to deleterious sequence variants in the *SLC2A1* gene.[1] This gene encodes the glucose transporter type 1 (GLUT1), which is primarily responsible for the entry of glucose into the central nervous system (CNS).[2] Loss of function of one of the *SLC2A1* alleles has been found to affect glucose transport, causing the disease.[1]

The so-called classic phenotype accounts for the majority of cases reported in the literature.[3-5] It is characterized by an onset in the first years of life, drug-resistant seizures, delayed psychomotor development, acquired microcephaly, spasticity, ataxia, and movement disorders.[6-8] Since it was first described and because of the identification of the genetic cause, the phenotypic spectrum has expanded considerably. In recent decades, a diverse group of related epileptic syndromes has been recognized.[9-16] Less severe forms have also been described, generally manifesting later in life.[5,7,17–19]

Historically, for patients with GLUT1DS there is a delay in the definitive diagnosis of 6 to 11 years.[4,5,20,21] The low prevalence of the disorder in daily practice, its wide phenotypic heterogeneity, and the lack of access to molecular studies may be the main reasons for this delay. Early diagnosis is important to start the ketogenic diet (KD), the current treatment of choice, as soon as possible. Early initiation of the KD has been shown to improve seizure control and overall outcome.[21–23]

The aim of this study was to provide a literature review on GLUT1DS with a focus on its clinical, molecular, diagnostic, and therapeutic characteristics.

CURRENT SITUATION OF GLUT1DS IN THE WORLD AND IN ARGENTINA

In the literature, highly variable incidence rates have been proposed for GLUT1DS, ranging from 1 in 90 000 to 1 in 24 000 live births.[13,24,25]

The Interdisciplinary Ketogenic Diet Therapy Team of Hospital Garrahan is currently seeing 6 patients diagnosed with GLUT1DS and estimates that there are at least 30 confirmed cases in our country (unpublished data). There is a clear gap between the estimated number of patients countrywide and the expected number based on international statistics. Considering the current Argentine population and assuming that the local incidence is within the international range, we would expect between 450 and 1670 individuals with the disorder countrywide.[26]

CLINICAL CHARACTERISTICS

GLUT1DS has a wide phenotypic spectrum, ranging from mild movement disorders to severe forms including encephalopathy, epilepsy, and delayed psychomotor development.

The classical phenotype (MIM #606777) is the most frequent and accounts for 85% of cases reported.[3–5] Patients classically present with early onset encephalopathy, drug-resistant seizure, delayed psychomotor development, and deceleration of head growth with acquired microcephaly. In addition, motor involvement, including ataxia, spasticity, and dystonia, is often observed.[5,7]

In recent years, the phenotypic spectrum of non-classical forms has markedly expanded; there are late-onset cases with mild psychomotor involvement, pure epileptic syndromes such as myoclonic atonic epilepsy or early onset absence epilepsy, and even patients without epilepsy, in whom permanent and paroxysmal movement disorders are the predominant manifestations.[5,7,17,27]

The most important clinical features are described below.

a. Epilepsy

GLUT1DS should be considered in the differential diagnosis of any patient presenting with early-onset epilepsy, especially when drug resistant, and associated movement disorders.[28]

Epileptic seizures have variable semiology and include focal and generalized seizures and even epileptic spasms.[4,8,20] Seizures are the first clinical sign in most patients and the main clinical concern in the first years of life, although they tend to resolve later in life.[29–32]

The interictal EEG is usually normal; however, according to age, different patterns may be observed: in infants, slowing and focal epileptiform activity is more frequent, while a generalized 2.5–

4 Hz spike-wave pattern is observed in children aged 2 years and older. An interesting feature, when present, is an abnormal preprandial EEG that improves with feeding as glucose is restored to the brain.[33,34]

It is important to note that GLUT1DS may be associated with different epileptic syndromes, including early onset absence epilepsy (10%), myoclonic atonic epilepsy (5%), and idiopathic generalized epilepsy (1%).[9,11-16]

b. Movement disorders

Movement disorders, whether or not associated with epilepsy, are suggestive of GLUT1DS.[4,5,30] These may be continuous and/or paroxysmal, and may change in response to different stressors, such as fasting, infections, prolonged exercise, and anxiety, among other emotions.

After seizures, the second most common symptom at onset are paroxysmal eye-head movements.[29,32,35] They are characterized by multidirectional and bilateral saccadic eye movements, usually accompanied by ipsilateral head movements.[35] Paroxysmal exercise-induced dyskinesia, episodes of alternating hemiplegia, and intermittent ataxia are also frequent. Myoclonus is usually of epileptic origin, although startle, action, and postural myoclonus has been less frequently reported.

Paroxysmal movement disorders usually intensify over time or may even develop during adolescence and adulthood.[30]

Persistent motor disorders may include spasticity, ataxia, and dystonia, which often result in gait disturbances. Chorea and tremor, though less frequently, may also be observed.[4,5,8,36,37]

c. Psychomotor development and cognitive function

In patients with GLUT1DS, intellectual disability is highly variable. Language delay and expressive language difficulties are frequently observed, possibly associated with speech impairment, such as dysarthria, learning difficulties, and cognitive impairment. The latter may be mild, moderate, or severe, but without a characteristic neuropsychological profile.[4,5,8,38] Cognitive impairment is usually proportional to the age of onset and the severity of the neurological manifestations.[4,5,32,39]

Behavioral disturbances, attention deficit, hyperactivity disorder, and depression may also be observed.[5,39,40]

d. Atypical manifestations

Atypical manifestations include writer's cramps, intermittent ataxia, total body paralysis, parkinsonism, and nocturnal muscle cramps in the legs.[41]

Less frequently, alternating hemiplegia of childhood, hemiplegic migraine, cyclic vomiting, and stroke-like episodes with transient hemiparesis, dysarthria, or aphasia have been described.[17,42–44]

Another rare manifestation of GLUT1DS is hemolytic anemia.[45–47]

e. Temporal pattern of clinical manifestations

Symptoms develop following a specific pattern according to the age and time of onset of the clinical manifestations: paroxysmal eye-head movements, along with seizures, are characteristic of onset in early infancy.[29,35] Developmental delay becomes increasingly evident and is followed by ataxia and exertion-induced dystonia, among other movement abnormalities that develop over time. Movement abnormalities generally are the main symptoms in adolescence and adulthood.[30,31] The time course of key clinical features of GLUT1DS is shown in *Figure 1*.

MECHANISM, MOLECULAR CHARACTERISTICS, AND INHERITANCE PATTERNS

GLUT1 is an integral membrane protein comprising 492 amino acids (*Figure 2a*). Its main function is to transport D-glucose between compartments (*Figure 2b*).[2] It is mostly expressed in erythrocytes, placental stromal cells, glial cells, and blood-brain barrier endothelial cells, where it facilitates the passage of glucose from the peripheral circulation to the CNS.[51–53]

The protein is encoded by the *SLC2A1* gene, which is located on the short arm of chromosome 1 and consists of 10 coding exons (1 and 10 partially) (*Figure 2c*).[54,55]

GLUT1DS occurs when, due to an alteration in the *SLC2A1* gene, the quality or quantity of the GLUT1 protein is not sufficient to ensure adequate supply of glucose to the CNS, affecting neurological function and development.[1,2] The severity of the clinical condition has been found to be inversely proportional to the residual GLUT1 activity and an activity lower than 25% is incompatible with life.[38,56–58]

While most GLUT1DS patients have a *de novo* heterozygous *SLC2A1* variant, about 10% have

one parent who is a carrier of the variant and therefore have an autosomal dominant inheritance pattern.[4,5,17,18,41,59,60] In addition, different cases of autosomal recessive inheritance have also been reported.[5,56,61]

The deleterious variants associated with GLUT1DS are distributed throughout the SLC2A1 gene, although most are found on exon 4, and some aminoacids are altered more frequently than others (*Figure 3*).[3–5,62]

Approximately 90% of the variants reported in patients affected with GLUT1DS involve one or a few base pairs of the *SLC2A1* gene.[5,17] More rarely, cases with large deletions or duplications, which may even involve the whole gene, have been reported.[5,17,65,66]

An association has been described between the pathogenic variant and the severity of the clinical condition, while no correlation has been found between the genotype and the response to the KD.[4,5,23,38] Nevertheless, it is important to mention that GLUT1DS has a great phenotypic heterogeneity and even patients with the same genotype may have very different clinical features.[5,59]

DIAGNOSIS

a. Cerebrospinal fluid analysis

Hypoglycorrhachia together with normal glucose levels is a distinctive biomarker for GLUT1DS.[3,38,67] Approximately 90% of patients have glucose levels below 40 mg/dL.[57,67,68] Lumbar puncture should be performed after 4 to 6 hours of fasting to stabilize glucose levels in the cerebrospinal fluid (CSF).[28,69] Peripheral blood glucose levels should be measured immediately before the lumbar puncture so that it is temporally related to glycorrhachia thus avoiding the hyperglycemia response to stress that may be associated with this maneuver.

The CSF/peripheral blood glucose ratio is also a useful diagnostic marker, being lower than 0.4 in most of the cases.[3,67]

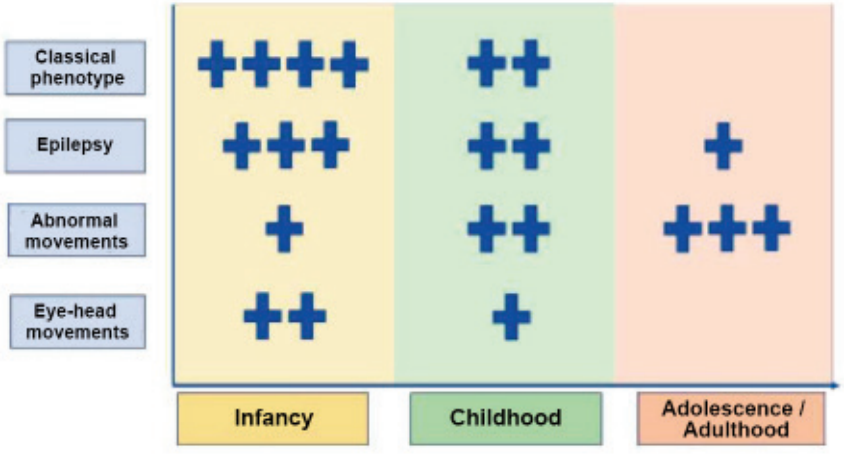
Patients with GLUT1DS have hypoglycorrhachia with normal or low CSF lactic acid levels, which helps to differentiate it from other conditions that are also associated with hypoglycorrhachia, such bacterial infections of the CNS and some mitochondrial conditions.[70–72]

The CSF features reported in a group of 157 patients with GLUT1DS by Leen et al. are summarized in *Table 1*.[68]

b. Study of the *SLC2A1* gene

Sanger sequencing of the *SLC2A1* gene is the molecular method of choice to characterize GLUT1DS. All 10 exons should be sequenced, including at least 10 specific flanking intronic bases of each of them. If sequencing is negative, gross deletions or duplications should be detected using a methodology sensitive to this type of variants, such as multiplex ligation-dependent probe amplification (MLPA).

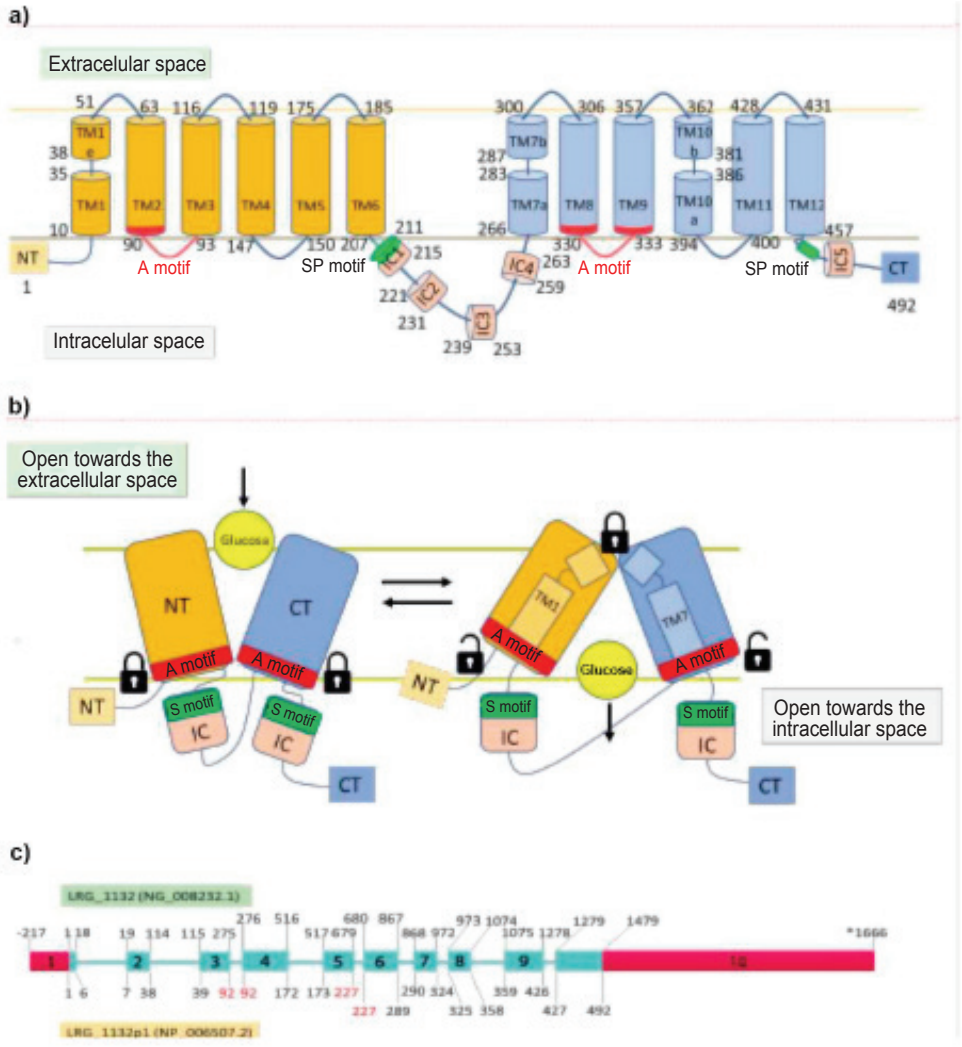
Figure 1. Schematic representation of the temporal pattern of main clinical manifestations in GLUT1DS patients



Very frequent: ++++.
Frequent: +++.
Moderately frequent: ++.
Rare: +.

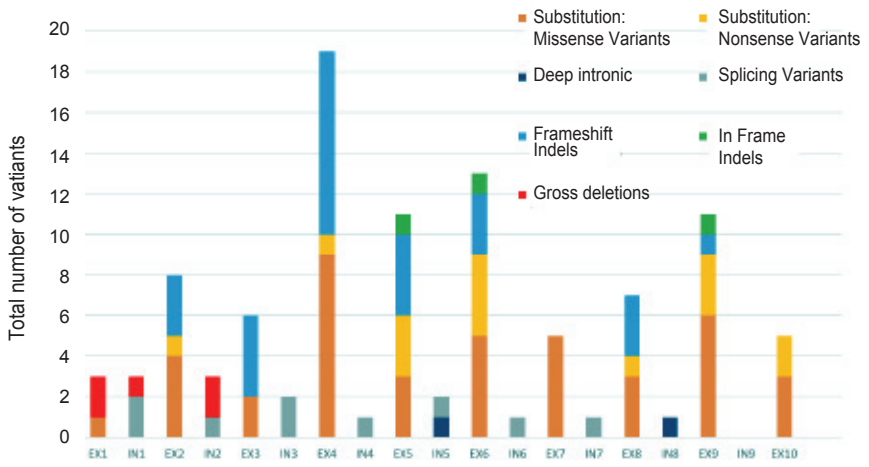
Massive parallel sequencing and comparative genomic hybridization offer the advantage of studying the *SLC2A1* gene together with a large number of genes, which may be useful for differential diagnosis purposes.[73] Nevertheless, in Argentina, access to these types of techniques is still limited and their cost is high compared to the standard Sanger/MLPA combination.[74]

Figure 2. Characteristics of the *SLC2A1* gene and GLUT1 protein



a) Topographic distribution of the GLUT1 protein in the plasma membrane. *The first 6 transmembrane segments* ***(TM1–TM6)*** *form the amino-terminal* ***(NT)*** domain. *The next 6 transmembrane segments* ***(TM7–TM12)*** *form the carboxy-terminal* ***(CT)*** domain. *The long intracytoplasmic segment connecting both domains contains 4 helices, or intracytoplasmic* ***(IC1–IC4)*** domains. *The* ***IC5*** *position in the CT end is not known exactly. GLUT1 has two proper signature motifs of the major facilitator superfamily (MFS), called* ***A motifs****. A copy between TM2 and TM3* ***(G_{84}LFVNRFGRR$_{93}$)*** *and another one between TM8 and TM9* ***(L_{32}5FVVERAGRR$_{334}$)****. Two signature motifs of the sugar transporter subfamily or* ***SP motifs*** *are also present, one copy in the NT domain, downstream of TM6* ***(P_{208}ESPR$_{212}$)*** *and one copy in the CT domain, downstream of TM12* ***(P_{208}ESPR$_{212}$)****.*[48,49] ***Simplified mechanism of transport.*** *The protein shifts between two structures, one with the cleavage of the glucose-binding protein toward the extracellular space and a second structure with the cleavage toward the cell interior. The former is stabilized by the formation of electrostatic interactions between the aminoacids positively charged in the A and SP motifs in each half of the protein, where IC domains also play a role. The second structure is stabilized by TM7 and TM1 interaction. The CT half provides most of the aminoacids involved in glucose binding, while the NT domain rotates to allow the passage between the alternative structures.*[48,49,50] *The energy necessary for transport is provided by the glucose gradient between compartments.*[2] ***Graphic representation of the* SLC2A1 *gene.*** *Exonic coding regions are represented by light blue boxes, while untranslatable regions are represented in red. In the upper part, positions of nucleotides are indicated at the boundaries of each exon. In the lower part, the range of encoded aminoacids is indicated. The position of those translated from codons formed from exon-exon splice junctions is marked in red.*

Figure 3. Distribution of variants along the *SLC2A1* gene reported to ClinVar, associated with GLUT1DS and classified as pathogenic or likely pathogenic, without conflicts in interpretation (102 total variants; database updated as of 7-14-2021)



Copy number variants are assigned to the exon/intron containing the first base involved. No gross duplications meeting these criteria are found in this database, suggesting that they are infrequent in GLUT1DS.[63,64]
EX: exon.
IN: intron.
Indel: insertion-deletion.

Currently, Hospital Garrahan offers the standard strategy for studying the *SLC2A1* gene to patients seen at the Department of Neurology who meet the clinical and CSF criteria for GLUT1DS.

Once the index case has been characterized and molecularly confirmed, it is advisable to perform genetic studies in the patient's parents to rule out the familial source of the disease.[60]

A small percentage of patients with a clinical diagnosis of GLUT1DS will have a negative molecular study of the *SLC2A1* gene.[75] It is possible that, in these cases, the pathogenic variant is located in gene regions not routinely studied, such as the promoter and deep intronic regions.[66,75,76] It has recently been proposed that pathogenic variants in other genes could cause a GLUT1DS-like symptoms, either by themselves or indirectly by disrupting *SLC2A1* function.[77,78]

DIAGNOSIS AND INITIAL MANAGEMENT OF GLUT1DS PATIENTS

Based on the data above, the following approach is proposed for the diagnosis and initial management of GLUT1DS patients (*Figure 4*).

SPECIFIC TREATMENT

The treatment of choice for GLUT1DS is the KD, a high-fat diet that induces a metabolic shift to nutritional ketosis. Increased ketone bodies in the blood, replace glucose as a carbohydrates and energy source for the CNS.[79,80]

The ketogenic diet therapy (KDT) should be initiated as soon as possible to obtain the best results even in the absence of a confirmatory molecular test.[21,22,81,82] A recent review on the efficacy of KDT in 270 GLUT1DS patients showed that epilepsy improved in 83% and that this effect was associated with age at treatment onset.[83]

Table 1. General characteristics of the cerebrospinal fluid obtained from 157 patients with GLUT1DS

Characteristic	Value
Cell count	Within the laboratory reference range
Protein levels	Within the laboratory reference range
Glycorrhachia	In the 16.2 to 50.2 mg/dL range (most < 40 mg/dL)
CSF/blood glucose ratio	In the 0.19 to 0.59 range (most < 0.4)
Lactic acid	Decreased or within the laboratory reference range

CSF/blood glucose ratio: the relationship of the glucose level in the cerebrospinal fluid and in peripheral blood.

Similarly, movement disorders and neurocognitive disorders also showed significant improvement with the KDT.[23,31,59]

Although a recent consensus on the use of the KDT for drug-resistant epilepsy has been published, there are specific considerations for the management of GLUT1DS patients with this approach (*Table 2*).[84]

The classic KD and the modified Atkins diet (MAD) have shown to be highly effective in the management of seizures resulting in a significant decrease in 80% and a reduction in the use of antiseizure medication in 64% of the patients.[22]

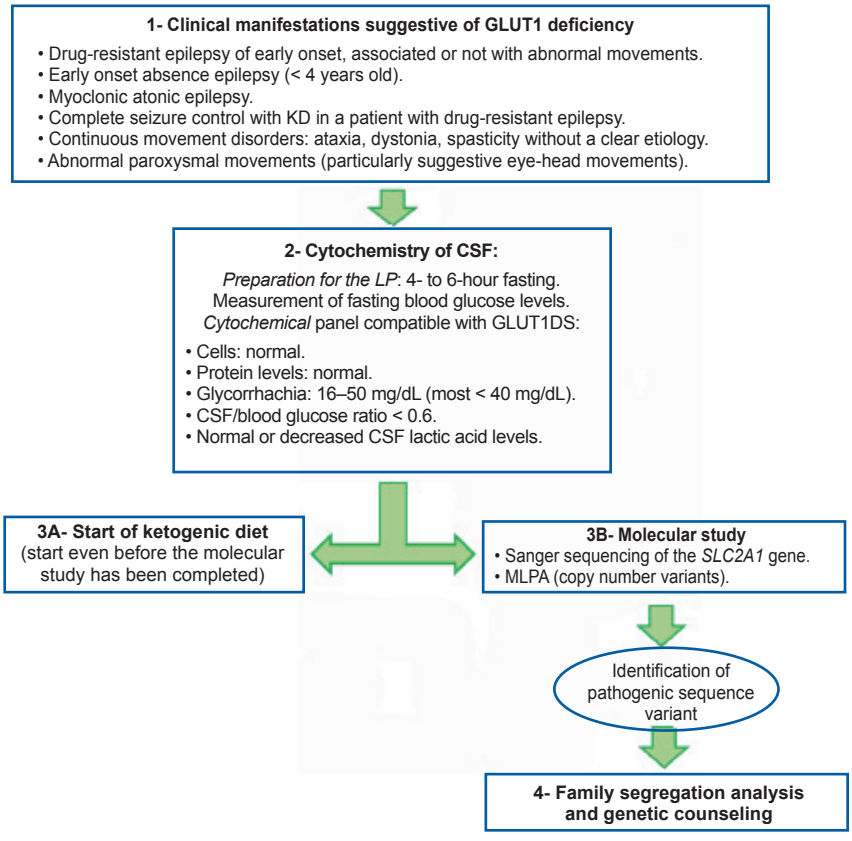
The classic KD generates high levels of ketosis and is preferred in young children, especially those under 3 years of age.[23] In adolescents and adults, the MAD may be indicated to improve adherence, compliance, and quality of life. The low glycemic index diet is not recommended because it provides very low ketones levels and there is no evidence of its benefit for GLUT1DS.[81]

Regarding the safety, studies show that most patients do not develop adverse effects.[83] Perhaps, the most frequently observed complication is failure to adhere to the diet in the long term.[83]

Treatment duration may be until adolescence and even into adulthood. To prevent long-term adverse effects of the diet, close nutritional and metabolic follow-up by specialists is advised.[85]

Regardless of the high efficacy that the KDT has demonstrated for the management of GLUT1DS, a certain percentage of these patients do not respond in terms of seizure and abnormal movement control, or achieving cognitive improvement.[83,86] Therefore, different treatments are being evaluated as potential complements to the KD. One of them is the triheptanoin, a

Figure 4. Diagnosis and initial management of GLUT1DS patients



KD: ketogenic diet
CSF: cerebrospinal fluid.
LP: lumbar puncture
CSF/blood glucose ratio: the relationship of the glucose level in the cerebrospinal fluid and in peripheral blood.
MLPA: multiplex ligation-dependent probe amplification.

synthetic triglyceride considered as a substrate to provide Krebs Cycle intermediates that cannot be supplied by glucose. This drug showed encouraging initial results when evaluated in small cohorts of patients, particularly in controlling the number and duration of motor and non-motor paroxysmal events.[87–89] However, a subsequent clinical trial did not show clinical efficacy in terms of seizure and movement disorder control.[90]

Another approach are oral ketones and ketone esters, which, although widely available on the market, have not been recommended for use in GLUT1DS.

A number of small molecules have been a source of interest due to their ability to enhance GLUT1 activity, such as alpha lipoic acid (thioctic acid), insulin-like growth factor-1 (IGF-1), hypoxia-inducible factor 1 alpha (HIF-1alpha), bone morphogenic protein 2 (BMP-2), and fibroblast growth factor 21 (FGF21).[91]

Lastly, gene therapy holds great promise for improving the quality of life of these patients in the near future. Promising results have recently been obtained in mouse and pig models treated with recombinant adenoviral vectors carrying a functional copy of the *SLC2A1* gene.[92,93]

CONCLUSION

GLUT1 deficiency syndrome has a broad clinical spectrum; however, there are manifestations that are highly suggestive of the disease, such as abnormal eye-head movements and drug-resistant seizures that begin early in life regardless of whether or not they are associated with abnormal movements.

The diagnosis is made based on CSF glucose levels in relation to blood glucose, and is confirmed by a comprehensive study of the *SLC2A1* gene. In cases in which the latter is positive, it will be extended to the parents of the index case in order to provide adequate family genetic counseling.

In the presence of a strong clinical suspicion, KDT should be initiated early, as it improves long-term prognosis, even prior to molecular confirmation, because the latter may take time or be negative in a small number of patients.

Early diagnostic suspicion, together with an adequate clinical characterization and the availability of the *SLC2A1* gene testing are crucial to reduce the time to diagnosis and accelerate the implementation of the most effective treatment.

Currently, in Argentina no statistical data on GLUT1DS are available; therefore, a national survey should be conducted to better understand so as to know with certainty what the situation of this disease in our country. ■

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Table 2. Comparison of indications and treatment recommendations with ketogenic therapy for neonatal drug-resistant epilepsy and Glut1 deficiency syndrome

Criterion	KD for neonatal drug-resistant epilepsy	KD for GLUT1DS
Indication:		
Epilepsy	Insufficient seizure control after 2 or more AEDs	First line of treatment
Movement disorder	Not indicated	First line of treatment
Psychomotor development	Not indicated	First line of treatment
Treatment		
Initiation	Optional	At diagnosis, at any age, as soon as possible
Duration	2 years or longer	Until adulthood
Ketosis and ketogenic ratio	Variable	The highest tolerable rate
LGID	Optional	Not recommended
Ketosis monitoring	In urine or blood	In blood
Measure carnitine levels	Optional	Recommended
Adverse effects monitoring	Recommended	Mandatory

KD: ketogenic diet
AEDs: antiepileptic drugs
LGID: low-glycemic index diet

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