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ORIGINAL ARTICLE

Glucose transporter type 1 deficiency syndrome (GLUT1DS): Characterization of a cohort treated with ketogenic therapy

Síndrome de deficiencia del transportador de glucosa tipo 1 (GLUT1DS): Caracterización de una cohorte tratada con terapia cetogénica

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

Glucose transporter type 1 deficiency syndrome (GLUT1DS) is a neurometabolic disorder characterized by refractory epilepsy, movement disorders, and low glucose concentration in cerebrospinal fluid. Ketogenic Diet Therapy (KDT) is the treatment of choice for seizure control in these patients.

What does this study contribute to what is already known?

This study provides clinical, biochemical, neurological, molecular, and nutritional background information on the Chilean cohort of patients with GLUT1DS at the time of diagnosis and follow up throughout therapy. It emphasizes the importance of early diagnosis and treatment with KDT in order to improve neurological prognosis.

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Abstract

Glucose transporter type 1 deficiency syndrome (GLUT1DS), caused by variants in the *SLC2A1* gene, causes conditions ranging from refractory epilepsy to movement disorders. Treatment consists of ketogenic therapy (KT). **Objective:** To characterize a cohort of patients with GLUT1DS undergoing KT, in follow-up at a national reference center in Chile. **Patients and Method:** A retrospective cohort study was conducted. Data were collected from clinical records, and the treating neurologists were consulted regarding phenotype, genotype, and clinical evolution following KT. A descriptive analysis was performed (median with interquartile range [IQR]) and Spearman correlation. **Results:** Nineteen patients were analyzed, with a median age of 7.3 years (IQR: 3.6-12.5). Symptom onset occurred at 0.5 years (IQR: 0.3-2.3); 16 patients presented with the classic phenotype. Eighteen patients (95%) experienced epileptic seizures, 12 (63%) had movement disorders, and 8 (42%) had language disorders. Diagnosis was established at 5 years (IQR: 0.6-7.5). In 16/19 patients, variants were identified in the *SLC2A1* gene. Significant negative correlations were observed between the interval from symptom onset to treatment initiation and the psychomotor development index ($r = –0.82$), verbal intelligence quotient ($r = –0.73$), and total intelligence quotient ($r = –0.68$). Following the initiation of KT, 14/19 patients became seizure-free, and 10/16 discontinued antiepileptic drugs. Modified KT (14/19) and malnutrition due to excess (11/19) predominated. Five patients developed mixed dyslipidemia. **Conclusion:** Ketogenic therapy was effective in managing epileptic seizures in GLUT1DS. Early diagnosis and timely initiation of KT should improve neurological prognosis.

Keywords:
Glucose Transporter type 1 Deficiency Syndrome;
Drug-Resistant Epilepsy;
Ketogenic Therapy;
Abnormal Movements

Introduction

Glucose transporter type 1 deficiency syndrome (GLUT1DS) (OMIM # 606777) is a neurometabolic disorder caused by variants in the *SLC2A1* gene, located on chromosome 1 (1p35-p31.3)[1]. This glucose transporter type 1 (GLUT1) is solely responsible for glucose entry into the central nervous system, and its haploinsufficiency affects brain function, causing refractory neonatal epilepsy and later-onset movement disorders[2]. The overall incidence is estimated at 1.65-4.1 per 100,000 newborns[3,4].

The classic phenotype, present in about 90% of patients, is characterized by onset before 2 years of age with seizures, neurodevelopmental delay, dysarthria, acquired microcephaly and/or movement disorders, apnea, and paroxysmal eye-head movements[5]. The non-classical phenotype includes manifestations such as paroxysmal dyskinesia without epilepsy, ataxia, dystonia, dysarthria, persistent tremor, and spasticity[6,7].

Patients with GLUT1DS have low glucose concentrations in cerebrospinal fluid (CSF) in the context of normal levels of blood glucose, with values < 40 mg/dL as the cut-off point, a relevant biological marker for suspecting this condition. However, mild phenotypes may have concentrations between 41 and 52 mg/dL[8,9]. It should be ruled out in patients with suggestive phenotypes, such as early-onset drug-resistant epilepsy, atypical absence seizures, or epilepsy with onset before age 4, epilepsy with tonic-myoclonic seizures, and epilepsy associated with movement disorders, especially paroxysmal eye-head movements.This condition should be ruled out even with CSF glucose levels above the established cut-off point[8,10].

Genetic analysis allows pathogenic variants in the *SLC2A1* gene to be identified in 80-90% of patients, and 10-15% have exon deletions or duplications (10,11). However, the absence of a pathogenic variant does not rule out the pathology[7,12].

Ketogenic diet therapy (KDT) is the first-line treatment because it provides ketone bodies as an alternative energy source for the brain, generated by a diet high in fat and very low in carbohydrates. It is important to note that KDT produces improvements in epileptic manifestations and in intellectual and social adaptive skills, but not in movement and language disorders[10,13-15].

In our country, there is only one report of two cases of patients with GLUT1DS, and there is a need to expand knowledge about this condition. The objective of this research is to present the first study that characterizes the Chilean cohort of patients with GLUT1DS treated with KT and followed up at a national reference center, INTA.

Patients and Method

Design

Retrospective cohort study between October 2021 and March 2022. Analyzed clinical, anthropometric, biochemical, and KDT data in patients with GLUT1DS

from the followed in our program at the INTA. All patients diagnosed up to the date of this study, referred from different health centers, and those who met the inclusion criteria were included. These patients are part of the National Complementary Food Program for Inborn Errors of Metabolism (PNAC-IEM, Ministry of Health), which provide them with ketogenic formula.

Inclusion criteria

Patients of any age diagnosed with GLUT1DS, by molecular study of the *SLC2A1* gene and/or by low glucose concentration in CSF with compatible clinical symptoms, were included. All patients were required to be at least 3 months on KT, have a record of fasting ketonemia (at least once a week), and have a registered record of nutritional intake.

Exclusion criteria

GLUT1DS patients with infectious, inflammatory, traumatic, and/or neoplastic conditions in the month before the study, or who had discontinued KDT, were excluded.

Neurological follow-up

Information was collected through the treating neurologists on phenotypic manifestations and use of antiepileptic drugs (AED) before and after starting KDT, and the results of the genetic study.

Psychometric evaluation

The results of the last assessment performed on each patient (between 2019 and 2022) were collected. The assessments were: Bayley Scales II in children under 42 months, from which the mental development index (MDI) and the psychomotor development index (PDI) were also recorded. For children over 42 months of age, Wechsler Scales were applied, all of which provided a verbal IQ and full-scale IQ[16-18]. Complementary indices were not considered due to their variability between different editions of the tests. In the group between 4 and 5 years 11 months, the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV) test was used. In children aged 6 to 18 years, the Wechsler Intelligence Scale for Children, Revised, third edition, and/or fifth edition (WISC-R, WISC-III, or WISC-V) tests were used. The expected score considered for age was between 90 and 110 for each parameter evaluated in the different tests[16-18].

Anthropometry

Weight and height were measured with minimal clothing, using a SECA electronic scale (+-0.1 kg), with the patient in the Frankfort plane in those older than 2 years. In children under 5 years of age, anthropometric evaluation included: weight for age (W/A), height for age (H/A), and weight for height (W/H) indexes, and in children over 5 years of age, body mass index (BMI/A) was used. National references based on WHO 2006-2007[19] were used.

KT classification

a.-Classic KDT (CKDT): fat and protein + carbohydrate ratio of 3-4:1, *b*.-Modified KDT (MKDT): ratio of 1.5-2.9:1, and *c*.-Modified Atkins Diet (MAD): ratio of 1-1.5:1 (10). All include medium-chain triglycerides (MCT) and essential fatty acids [docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)][20]. For this study, inadequate adherence to the KT was defined as compliance of < 50% and fair compliance of < 75% for more than 3 consecutive days.

Dietary intake

The last 24-hour recall diet intake registry recorded from the clinical record before the study was used. Energy, macronutrient, calcium, and vitamin D intake were analyzed using Aminoacid Analyzer software (V1.0.0.0, 2015). This was compared with the FAO/WHO/UNU recommendations[21] for energy and the Recommended Dietary Allowance (RDA) for calcium and vitamin D[22]. In addition, adequate consumption was defined between 90% and 110% of the recommended intake. Furthermore, as part of the INTA follow-up protocol, patients with KDT should be supplemented with L-carnitine, starting with a dose of 20 mg/kg/day, which should be adjusted according to plasma levels to maintain a ratio of free to esterified carnitine ≥ 1.

Biochemical parameters

CSF glucose concentrations were obtained from clinical records, following published protocols and cut-off points (23). Blood ketone and glucose concentrations were determined using a blood glucose meter. This analysis allows monitoring of GLUT1DS patients to ensure that their values remain within the optimal therapeutic range, which is 2-5 mmol/L for ketones and 60-90 mg/dL for blood glucose[10]. In addition, samples were sent to an external laboratory to determine the level of 25-OH vitamin D (25-OHD) using an electrochemiluminescence immunoassay (deficiency ≤ 20 ng/mL, insufficiency 21-29 ng/mL, and optimal 30-50 ng/mL)[24], and the serum lipid profile was evaluated by enzymatic method, considering total cholesterol levels (acceptable < 170 mg/dL, borderline-high 170-199 mg/dL, and high ≥ 200 mg/dL), HDL (acceptable > 45 mg/dL, borderline-high 40-45 mg/dL, low < 40 mg/dL), LDL (acceptable <110 mg/dL, borderline-high 110-129 mg/dL, high ≥ 130 mg/dL), triglycerides (acceptable < 75 mg/dL for children under 9 years of age

or 90 mg/dL for children over 9 years of age, borderline-high 75-99 mg/dL or 90-129 mg/dL, high ≥ 100 mg/dL or ≥ 130 mg/dL, respectively)[25]. Carnitine levels were assessed by the Metabolic Diseases Laboratory using tandem mass spectrometry: total carnitine (normal 36-56 µmol/L), free carnitine (normal 19-35 µmol/L), and esterified carnitine (normal 4-14 µmol/L).

Statistics

STATA 17 software was used. Descriptive data are presented as median with interquartile range (IQR: p25-p75). The cohort was divided into two groups: those evaluated by Bayley II and those by Wechsler; the Mann-Whitney tests were applied in each group to search for associations between clinical, genetic, and treatment variables with the results of the cognitive tests. In addition, Spearman's correlation was performed between quantitative variables.

Ethical considerations

This study was approved by the INTA Ethics Committee (April 14, 2021). Parents and/or caregivers signed informed consent, and children over 8 years of age signed an informed assent.

Results

Characteristics of the study cohort

19 patients with GLUT1DS were included, with an age of 7.3 years (IQR: 3.6-12.5). Of the total, 11 were male (Table 1).

Clinical findings at diagnosis

The age of symptom onset was 0.5 years (IQR: 0.3-2.3). In 14/19 patients, a lumbar puncture was performed at the time of clinical suspicion of the syndrome, finding a CSF glucose concentration of 30 mg/dL (IQR: 28.8-31) and a CSF/serum glucose ratio of 0.34 (IQR: 0.3-0.4).

According to the phenotypic classification, 16/19 had a classic type deficiency. In addition, 18/19 patients had epileptic seizures at the time of diagnosis, with generalized, tonic-clonic (6/19), and absence (6/19) seizures predominantly. Only one patient was suspected due to ataxia and abnormal eye movements. In addition, 12/19 had movement disorders, 8/19 had language disorders, and 7/19 had microcephaly. Before starting KT, 16/19 were receiving AED.

The diagnosis was made at 5 years of age (IQR: 0.6-7.5). Regarding genotype, 16/19 patients had a pathogenic variant: 8 with a missense mutation, 5 with a frameshift mutation, 2 with a nonsense mutation, and 1 with a deletion in exon 1. No variants were found in the *SLC2A1* gene in 2 patients, but both had low glucose concentrations in CSF and clinical manifestations consistent with the syndrome.

Cognitive assessment

Table 2 summarizes the results of the psychometric evaluations performed in 15 patients in the cohort. An 8-year-old patient was assessed using a developmental scale with an age range lower than her chronological age in order to obtain her cognitive performance due to developmental delay. Spearman's correlation analysis revealed a significant negative correlation between the PDI and the time elapsed from symptom onset to the start of KDT ($r = -0.82$, $p = 0.046$). This result was also observed for the verbal IQ ($r = -0.78$, $p = 0.014$) and for the full-scale IQ ($r = -0.81$, $p = 0.008$) (Figures 1-3).

Implementation, clinical response, and monitoring of KDT

KT was initiated within 0.3 months (IQR: 0.1-0.7) after diagnosis. However, the period from symptom onset to initiation of diet therapy was 1.8 years (IQR: 0.2-5.5).

According to neurological history, after starting KDT, 14/19 patients were seizure-free, 3/19 had a 90% reduction in seizures, and 1/19 had a 50% reduction. In addition, 10/16 patients discontinued medication, and 3/16 reduced it. Regarding non-epileptic manifestations, those who had been on KDT for more than one year (16/19 patients) presented a decrease in eye and involuntary movements and hypotonia, or they disappeared, but there were no measurable changes in language impairment.

Table 3 details the nutritional characteristics of the cohort at the time of this study. It was observed that most patients followed a MKDT and were predominantly overweight. Only two patients showed growth retardation, with a Z score of H/A < -2 SD. The PNAC-IEM ketogenic formula was consumed by 17/19 patients. In addition, three patients were classified as having inadequate adherence to diet therapy, two of whom were adolescents with a late diagnosis. Moreover, 22% of the total energy consumed (%E) came from MCT. Additionally, in the evaluation of nutritional intake, it was identified that 3 and 8 patients from different age groups did not meet calcium and vitamin D requirements, respectively.

Of the 19 patients, analysis of serum 25-OHD levels revealed 2 patients with insufficient levels and 2 with deficient levels (Table 4). When the intake data were cross-referenced with serum levels, it was observed that 3 of the 4 patients with low 25-OHD levels did indeed have a deficient dietary intake of vitamin D. The remaining case with insufficient vitamin D levels reported adequate intake.

Table 1. Demographic characteristics of the cohort of patients with GLUT1DS receiving ketogenic diet therapy (n = 19)

Sex, n	11 males, 8 females
Age at symptom onset, years, median (IQR)	0.5 (0.3-2.3)
Age at diagnosis, years, median (IQR)	5 (0.6-7.5)
Age at initiation of KDT, years, median (IQR)	5 (0.6-8.1)
Age at time of study, years, median (IQR)	7.3 (3.6-12.5)
- Under 42 months, n (%)	6/19 (31.6%)
- Over 42 months, n (%)	13/19 (68.4%)
Patients who underwent lumbar puncture, n (%)	14/19 (73.7%)
- CSF glucose concentration, mg/dL, median (IQR)	30 (28.8-31)
- CSF/serum glucose ratio, median (IQR)	0.34 (0.3-0.4)
Phenotype, n (%)	
- Classical	16/19 (84.2%)
- Non-classical	3/19 (15.8%)
Clinical manifestations, n (%)	
- Movement disorders	12/19 (63.1%)
- Language disorders	8/19 (42.1%)
- Microcephaly	7/19 (36.8%)
Patients using antiseizure medications prior to KT, n (%)	16/19 (84.2%)
Genotype, n (%)	16/19 (84.2%)
- Missense	8/16 (50%)
- Frameshift	5/16 (31.3%)
- Nonsense	2/16 (12.5%)
- Exon deletion	1/16 (6.3%)

GLUT1DS, glucose transporter type 1 deficiency syndrome; KDT, ketogenic diet therapy; CSF, cerebrospinal fluid.

Table 2. Cognitive assessment results in patients with GLUT1DS (n = 15)

Cognitive development assessment tests	n (%)
Bayley Scales II[a] (n: 6)	
MDI	
- Below expected for age (< 90)	5/6 (83.3%)
- Within expected range for age (90-110)	1/6 (16.7%)
PDI	
- Below expected for age (< 90)	6/6 (100%)
- Within expected range for age (< 110)	0/6 (0%)
Wechsler Intelligence Scales (WPPSI-IV, WISC-R, WISC-III and WISC-V)[a] (n: 9)	
VIQ	
- Below expected for age (< 90)	7/9 (77.8%)
- Within expected range for age (90-110)	2/9 (22.2%)
FSIQ	
- Below expected for age (< 90)	7/9 (77.8%)
- Within expected range for age (90-110)	2/9 (22.2%)

GLUT1DS, glucose transporter type 1 deficiency syndrome; MDI, Mental Development Index; PDI, Psychomotor Development Index; VIQ, Verbal Intelligence Quotient; FSIQ, Full Scale Intelligence Quotient. aExpected results were defined according to the patient's age for the Bayley II[16] and Wechsler Intelligence Scales[18].

According to the INTA follow-up protocol, L-carnitine supplementation is indicated for all patients at the start of KT. 16/19 patients received this supplementation. No free carnitine deficiency was observed, and 13/16 patients maintained a free/esterified carnitine ratio > 1 (Table 4).

Regarding the annual lipid assessment suggested by the INTA protocol, 5/19 patients presented mixed dyslipidemia. In addition, one patient had isolated hypercholesterolemia, another had isolated hypertriglyceridemia, and 3 patients had low HDL (Table 4).

Discussion

This is the first local report of a cohort with this syndrome, as INTA is the national reference center for the delivery of the ketogenic formula, and all patients with GLUT1DS are referred there. Since its description in 1991 by Dr. Darryl C. De Vivo, GLUT1DS has been extensively studied, with more than 300 articles characterizing its phenotype and genotype in people undergoing long-term treatment[26]. The diagnosis is confirmed when a variant in the gene is identified, along with low glucose concentration in CSF and symptoms

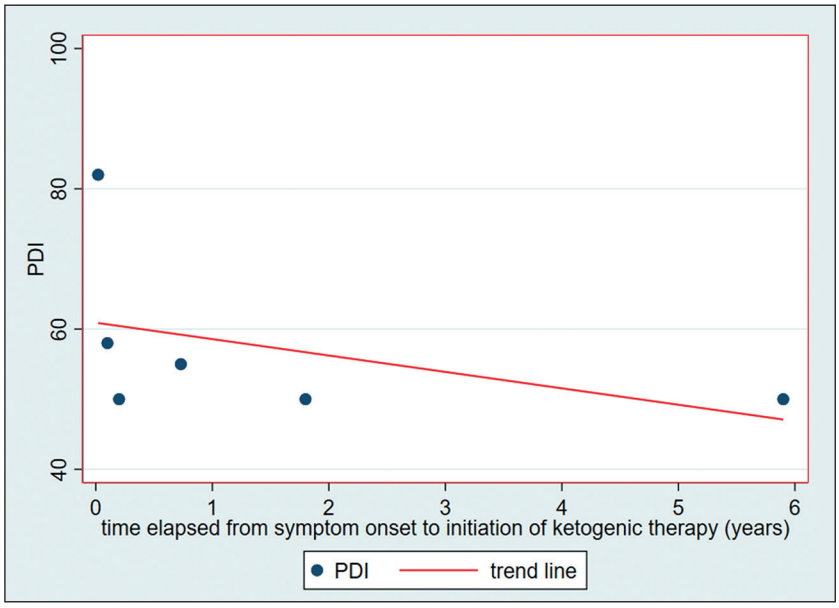

Figure 1. Spearman correlation between the psychomotor development index and the time elapsed from symptom onset to initiation of ketogenic therapy (n = 6).

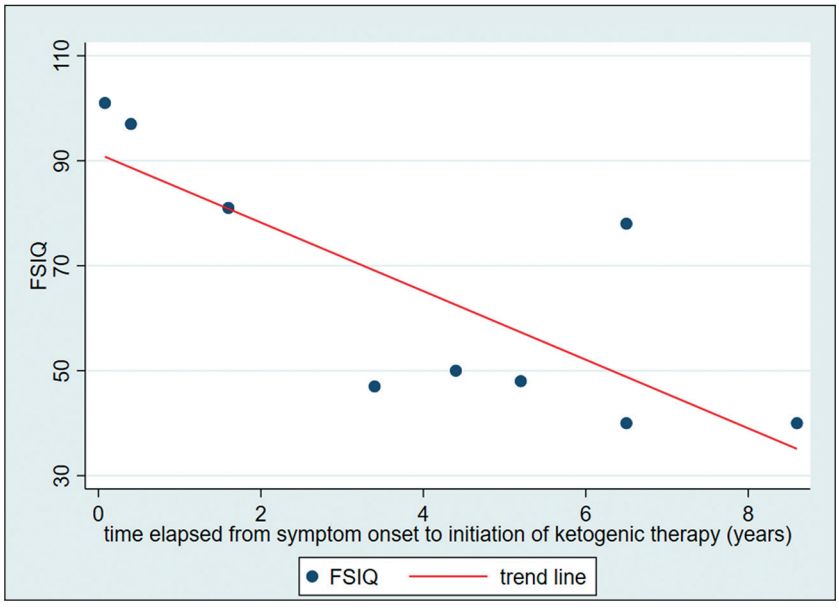

Figure 2. Spearman correlation between full-scale intelligence quotient and the time elapsed from symptom onset to initiation of ketogenic therapy (n = 9).

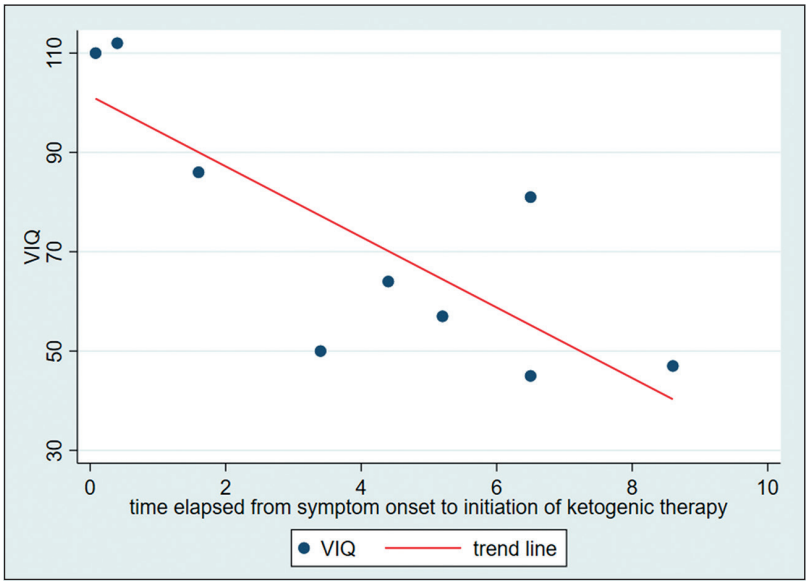

Figure 3. Spearman correlation between verbal intelligence quotient and the time elapsed from symptom onset to initiation of ketogenic therapy (n = 9).

Table 3. Nutritional characteristics of patients with GLUT1DS receiving ketogenic diet therapy (n = 19)

Time on KDT, years, median (IQR)	3 (1.5-4.5)
Type of ketogenic therapy, n (%)	
- CKDT	2/19 (10.5%)
- MKDT	14/19 (73.7%)
- MAD	3/19 (15.8%)
Nutritional status[a], n (%)	
- Risk of undernutrition	2/19 (10.5%)
- Normal	6/19 (31.6%)
- Overweight	9/19 (47.4%)
- Obesity	2/19 (10.5%)
Energy	
- kcal/day, median (IQR)	1551.3 (1135.5-2018.7)
- kcal/kg/day, median (IQR)	59.1 (47.1-76.4)
- Adequacy %[b], median (IQR)	94.6 (83.2-105.4)
Protein	
- g/day, median (IQR)	44.8 (30.5-70.4)
- g/kg/day, median (IQR)	1.8 (1.4-2)
- P %, median (IQR)	11.6 (9.8-15.1)
Carbohydrates	
- g/day, median (IQR)	24.2 (12.6-37.6)
- CHO%, median (IQR)	7.0 (3.1-8.8)
Fat	
- g/day, median (IQR)	138 (98.6-181.1)
- F%, median (IQR)	81.9 (77.1-83.8)
Calcium	
- mg/day, median (IQR)	1088 (919.5-1723.8)
- Adequacy %c, median (IQR)	127.7 (96.8-144.2)
Vitamin D	
- IU/day, median (IQR)	600 (477-1058)
- Adequacy %c, median (IQR)	100 (80-176.3)
L-carnitine supplementation (n = 16) mg/kg/day, median (IQR)	54 (26.1-75.7)

GLUT1DS, glucose transporter type 1 deficiency syndrome; KDT, ketogenic diet therapy; CKT, classical ketogenic therapy; MKT, modified ketogenic therapy; MAD, modified Atkins diet; IU, international unit. [a]Nutritional status according to WHO 2006–2007[19]: risk of undernutrition (weight-for-height or BMI-for-age Z-score ≤ –1), normal (Z-score –1 to 1), overweight (Z-score ≥ 1), obesity (Z-score ≥ 2). [b]Energy adequacy according to FAO/WHO/UNU requirements[21] and [c]calcium and vitamin D adequacy according to the Institute of Medicine[22].

Table 4. Biochemical parameters of patients with GLUT1DS on a ketogenic diet therapy (n = 19)

Glucose, mg/dL, median (IQR)	76.5 (66.5-80)
Ketonemia, mmol/L, median (IQR)	2.4 (2-2.9)
Vitamin D, ng/mL, median (IQR)	33.9 (30.4-45.9)
- Deficient, n (%)	2/19 (10.5%)
- Insufficient, n (%)	2/19 (10.5%)
- Optimal, n (%)	15/19 (78.9%)
Total carnitine, µmol/L, median (IQR)	82 (57-100)
Free carnitine, µmol/L, median (IQR)	40 (32.5-52)
Esterified carnitine, µmol/L, median (IQR)	43 (24-51.5)
Free/esterified carnitine ratio, median (IQR)	1.1 (0.7-1.6)
Total cholesterol, mg/dL, median (IQR)	148 (137-174.5)
- Acceptable, n (%)	14/19 (73.7%)
- Borderline-high, n (%)	3/19 (15.8%)
- High, n (%)	2/19 (10.5%)
HDL cholesterol, mg/dL, median (IQR)	55.7 (43.5-67.3)
- Acceptable, n (%)	14/19 (73.7%)
- Borderline-high, n (%)	1/19 (5.3%)
- Low, n (%)	4/19 (21%)
LDL cholesterol, mg/dL, median (IQR)	79 (64.7-100.8)
- Acceptable, n (%)	15/19 (78.9%)
- Borderline-high, n (%)	3/19 (15.8%)
- High, n (%)	1/19 (5.3%)
Triglycerides, mg/dL, median (IQR)	56 (49-88)
- Acceptable, n (%)	12/19 (63.1%)
- Borderline-high, n (%)	4/19 (21%)
- High, n (%)	3/19 (15.8%)

GLUT1DS, glucose transporter type 1 deficiency syndrome.

suggestive of the pathology. However, the absence of a variant in the gene does not rule out the syndrome, as long as there is a low concentration of glucose in the CSF and two or more suggestive clinical symptoms are detected[10].

In our cohort, of the 14 patients who underwent lumbar puncture, two did not have a variant in the *SLC2A1* gene but had a CSF glucose/blood glucose ratio of < 0.4 and had suggestive clinical symptoms (epilepsy and movement disorder) and responded positively to KDT, consistent with the 2022 consensus[10]. In addition, one patient had a sister with a confirmed diagnosis and presented with clinical features compatible with GLUT1DS, as previously published patients[27]. With the second child, it was decided to study the mother, and the c.694C>T variant, associated with a late-onset form, was identified. The mother had abnormal movements during her pregnancies, but has been asymptomatic the rest of the time and has never used KDT.

Around 250 pathogenic variants have been described in the *SLC2A1* gene, with *de novo* variants predominating[6]. Variants with premature stop codons (*nonsense*) and frameshift mutations have been associated with a 50% loss of GLUT1 activity and are related to the classic phenotype. Late-onset forms have been associated with missense variants, with 50% and 70% activity[28]. In our series, patients who had variants with premature stop codons or frameshift mutations were all classified as having the classic presentation. Of those with a missense variant, 63% (6/9 cases) had a classic presentation. Of the 16 mutations found, 67% have been reported as pathogenic, and 6 have been in the European population[29-34].

The recent GLUT1DS consensus states that drug-resistant seizures are the first sign, mostly generalized seizures. The second most frequent sign is the distinctive paroxysmal eye-head movements, and movement disorders such as spasticity, ataxia, and dystonia[10]. In a study of 270 GLUT1DS patients, 82% had epilepsy, 66% had movement disorders, with ataxia being the most commonly observed;

59% had cognitive impairment, and 34% had microcephaly[35].

The infant brain can require up to 80% of daily energy, and due to its limited glycogen storage, KDT is the treatment of choice as it provides ketone bodies as an alternative energy source, which explains its effectiveness in controlling seizures and reducing AED[36]. A study, which included 270 GLUT1DS patients, reported that 52% of patients were seizure-free, 82% of patients had movement disorders that disappeared or improved, and cognitive assessment improved in 59% of 58 patients[35]. Other studies report a significant reduction or discontinuation of AED use[37,38]. In our case series, similar results were observed in terms of seizure control and AED use. It is important to emphasize that of the 16 patients using AED, 62.5% discontinued treatment because there was 100% seizure control. In addition, we observed clinical improvements in eye and involuntary movements and hypotonia.

In relation to neuropsychological assessments, during clinical follow-up, most patients had cognitive development below what was expected for their age. In addition, a negative correlation was observed between some of the cognitive test indexes and the time interval between symptom onset and KDT. Although these are standardized, validated tools used to determine cognitive development, they alone are not enough to determine actual intellectual abilities in this pathology, suggesting that they should be complemented with others that assess performance and adaptive behavior in other areas, in order to determine more specific patient requirements. In addition, there is a lack of objective and standardized assessment of language skills[39]. It is important to start KDT even in the presence of clinical and/or biochemical suspicion without a confirmed diagnosis, as early initiation of KDT is a predictive factor for cognitive outcomes, improving intellectual and social skills[10].

Carnitine is crucial for optimizing the beta-oxidation of long-chain triglycerides in the mitochondria and maintaining ketogenesis[40]. Although there is no consensus, supplementing with carnitine is recommended when the free carnitine value is decreased[10]. Carnitine deficiency has been observed by 68% of the professionals surveyed who implement KDT in GLUT1DS[41]. One article reported a deficiency in 6/18 patients after one month of KDT, with subsequent long-term normalization[42].

Regarding some complications of KDT, our study detected vitamin D deficiencies in some patients, mainly associated with poor adherence to the diet. Additionally, it has been reported that AEDs have a deleterious effect on bone architecture[43,44]. Two studies evaluated 25-OHD levels, one of which detected 3/18 cases and the other 6/26 cases that reported vitamin D deficiency at the start of diet therapy, a situation that reversed during follow-up[42,45].

Furthermore, in our group, some patients presented alterations in their lipid profile. A study that evaluated the lipid profile in 34 patients after 5 years of starting KDT did not observe significant changes[37].

The study has strengths, such as being the first local report on GLUT1DS patients. Its approach consists of a well-defined cohort by the reference center for the delivery of the ketogenic formula, which ensures consistent data and a comprehensive assessment of the condition. The results showing the efficacy of KDT in controlling seizures and reducing AED use, together with the correlation between early treatment initiation and better cognitive outcomes, are crucial.

However, it also has weaknesses. A sample of 19 patients limits the generalization of the findings, so our associations are exploratory. However, it is a rare syndrome, but the results are still consistent with international evidence. In addition, it is a retrospective study, so there is the possibility of bias in data collection. A specific limitation is the lack of head circumference measurement.

In conclusion, this study allowed us to characterize Chilean patients with GLUT1DS clinically, genetically, and therapeutically, highlighting the importance of early diagnosis and the initiation of KDT as early as possible. The classic form of the disease was predominant, with epileptic seizures and movement disorders. In addition, KDT was highly effective in controlling seizures and reducing AED use, with acceptable adherence and no significant complications.

Current research focuses on diagnosis in the neonatal period[46], as evidence suggests that early suspicion and early initiation of KT are associated with a better neurological prognosis. Likewise, it emphasizes multidisciplinary follow-up focused on detecting nutritional deficiencies and neurological alterations not associated with the pathology in order to optimize the patient's quality of life.

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.

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