Glucose transporter type 1 deficiency syndrome (GLUT1-DS) was first described by De Vivo in 1991, and the classic clinical manifestations include infantile epilepsy, developmental delay, and acquired microcephaly. A neurological complex disorder including elements of hypotonia, spasticity, ataxia, and dystonia can frequently be present. GLUT1-DS is an inborn error of metabolism caused by impaired glucose transport through blood–brain barrier in the majority of patients because of mutation of solute carrier family 2 (facilitated glucose transporter) member 1 gene (SLC2A1), encoding the transporter protein. We report a 6-year-old girl with GLUT1-DS, which is caused by a novel heterozygous variant c.109dupC of the SLC2A1 gene. The dominating clinical features were ataxia, epilepsy started at 4 years, acquired microcephaly, and mild intellectual disability. Treatment with ketogenic diet showed clinical improvement with the reduction of ataxia and seizure control in a 10-month follow-up period.

**Keywords:** Glucose transporter type 1 deficiency syndrome, ketogenic diet, movement disorder, SLC2A1 gene

**INTRODUCTION**

Glucose transporter type 1 deficiency syndrome (GLUT1-DS) was first described in 1991 by De Vivo, who identified in the deficiency of glucose transport through the blood-brain barrier the cause of persistent hypoglycorrhagia, convulsions and developmental delay in two patients. The classic GLUT1-DS manifestations include infantile seizures, acquired microcephaly, developmental delay, hypotonia, and a complex movement disorder including elements of dystonia, spasticity, and ataxia. The clinical spectrum has been recently broadened to also include sporadic and familial paroxysmal exercise-induced dyskinesia with or without epilepsy and different degrees of cognitive impairment associated with dysarthria, disfluency, and expressive language deficits.

GLUT1-DS is an inborn error of metabolism caused by impaired glucose transport through blood–brain barrier in the majority of patients as a result of mutation of the solute carrier family 2 (facilitated glucose transporter) member 1 gene (SLC2A1), mapped to the short arm of chromosome 1 (1p34.2). SLC2A1 de novo mutations are the most frequently detected mutation. Familial cases are due to autosomal-dominant inheritance with complete penetrance; however, a case of autosomal-recessive transmission has also been described. All detected mutations are heterozygous as homozygous mutations are presumably lethal in utero. The distinctive biomarker for GLUT1-DS is low cerebrospinal fluid (CSF) glucose concentration in the presence of normoglycemia, and CSF/blood glucose ratio usually is less than 0.4 (range, 0.19–0.59). A molecular analysis of SLC2A1 gene can confirm the diagnosis. Approximately 70%–80% of patients carry SLC2A1 mutations.

We describe the phenotype of a 6-year-old girl with GLUT1-DS with a novel heterozygous variant c.109dupC of SLC2A1.
CASE PRESENTATION

The patient, a 6-year-old girl with unremarkable family history, was the only child of non-consanguineous Caucasian parents. She was born at 39th week of gestation by cesarean section because of mild fetal distress. Apgar Score was 8 (1’) and 9 (5’), birth weight was 2880 g, and head circumference (HC) was 34 cm (25–50° percentile [pc]). There was a mild psychomotor delay: head control at 4 months, gait at 30 months, first words at 12 months, language was dysarthric, daily sphincteric control at 4 years, whereas the overnight control was not yet acquired. At 4 months, a diagnosis of gastroesophageal reflux and esophageal duplication was made. Epileptic seizures started at the age of 4 years and 8 months with two prolonged generalized tonic–clonic seizures, during wakefulness, lasting less than 10 min, and stopped by intrarectal diazepam. The seizures recurred within a month. At the same time, parents noticed absence seizures lasting about 1–4 s several times a day. Interictal wakefulness EEG was reported as normal. Brain and spinal cord magnetic resonance imaging, performed at 4 years 10 months, showed minimal and non specific incomplete myelination. She was started on sodium valproate (VPA) with generalized tonic–clonic seizures control but absence seizures persisted. When she arrived to our clinic for the first time, she was 4 years and 11 months old. Neurological examination showed microcephaly (HC, 48 cm, <3rd pc), mild dysarthria, and ataxic gait with mild distal spasticity of the lower limbs. Cognitive function testing at 5 years with Wechsler Adult Intelligence Scale showed mild intellectual disability (intelligence quotient [IQ], 55). Awake electroencephalography (EEG) showed diffuse spike and wave abnormalities on a normal background activity; intermittent photic stimulation and hyperpnea was normal. Several absence seizures with fixed gaze, lasting 3–4 s were recorded [Figure 1]. EEG during sleep showed epileptiform abnormalities in frontal region [Figure 2]. Ethosuximide was added to VPA with partial control of absence seizures. Biochemical analysis of CSF disclosed a low glucose concentration of 1.72 mmol/L (normal range, 2.78–3.89 mmol/L) and reduced CSF/blood glucose ratio of 0.26 (normal range, >0.6) with normal plasma glucose level of 6.5 mmol/L (normal range, 4.4–6.6 mmol/L). The genomic DNA isolated from peripheral blood and analyzed by polymerase chain reaction (PCR) of the coding exons of the SLC2A1 gene and direct sequencing revealed a novel heterozygous variant c.109dupC. [p.(Gln37Profs*52)]. The detected variant is not included in the database of short genetic variation (dbSNP) or other clinical variation databases (ClinVar, Exome Aggregation Consortium Browser, and Human Gene Mutation Database). Parental genotype analysis confirmed the variant being de novo. Treatment with classic ketogenic diet (KD), ratio 4:1, was initiated at 5 years and 6 months of age. Beta-hydroxybutyrate blood levels were durably maintained between 3 and 5 mmol/L. After a few days of treatment with KD, the patient showed clinical improvement with reduction of ataxia, dysarthria, and seizure freedom, even after

Figure 1: Ictal awake EEG: generalized spike–slow wave complexes, lasting 3–4 s (absence), on a normal background activity
Approximately 70%–80% of patients with GLUT1-DS carry SLC2A1 gene mutations. In our patient, PCR of the coding exons of the SLC2A1 gene revealed a novel heterozygous variant c.109dupC [p.(Gln37Profs*52)], not included in the dbSNP or other clinical variation databases.

The identified variant is a “frameshift insertion” that causes a transcript-reading error resulting in premature termination of protein synthesis. Therefore, we could hypothesize that the mutation causes a haploinsufficiency, compatible with GLUT1 deficiency.

The distinctive biomarker for GLUT1-DS is low CSF glucose concentration or hypoglycorrhachia in the presence of normoglycemia, in fact in our patient, biochemical analysis of CSF showed a low glucose concentration and reduced CSF/blood glucose ratio.

Recently, the clinical spectrum of GLUT1-DS has been broadened to include developmental delay and movement disorders without epilepsy. In our patient, psychomotor delay and ataxic gait were reported since first months of life, associated with acquired microcephaly, but GLUT1-DS was suspected only after the epileptic seizure onset.

Epilepsy is still considered the main clinical feature in the classic phenotype of GLUT1-DS, it usually starts during infancy with a mixture of different types. In our patient, epilepsy started later than the average onset of the classic phenotype, with two tonic–clonic seizures and absences at the age of 4 years and 8 months.

In our opinion, according to recent description of non classical phenotypes, GLUT1-DS should be early considered in children presenting developmental delay, ataxia, and movement disorders, even without epilepsy.

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Conflicts of interest
There are no conflicts of interest.

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