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RESEARCH ARTICLE

Rare Presentations of GLUT1 Deficiency Syndrome: Rare Variants With Cortical Dysplasia in Two Unrelated Families

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ABSTRACT

Glucose transporter type 1 deficiency syndrome (GLUT1DS) affects all age groups, from infants to adolescents, and involves age-specific symptoms. Nonclassic GLUT1 DS is observed in 10% of cases, in which seizures are not observed, and the condition involves a milder accompanying phenotype and paroxysmal dyskinesias. Cranial imaging findings in cases of GLUT1 DS are variable. The purpose of this report is to describe rare genetic variants in two cases of GLUT1 DS with cortical dysplasia detected at magnetic resonance imaging (MRI) and exhibiting differing clinical presentations and to discuss the relationship between them. Two cases presenting to the Balıkesir University Medical Faculty paediatric neurology clinic, Türkiye, between 01.08.2019 and 01.12.2024 due to seizures and inability to speak/numbness in the hands and arms, diagnosed as GLUT1 DS, and with cortical dysplasia, were included. The patients' files, MRI and physical examination findings and family pedigrees were evaluated. We detected two different pathogenic and likely pathogenic variants in *SLC2A1* (NM_006516.3) in patients from unrelated families. Patient 1 exhibited a heterozygous c. 1208C > T variant and patient 2 a heterozygous likely c. 278G > A variant. In conclusion, the careful evaluation of patients with structural brain damage and determination of the molecular aetiology of underlying inherited metabolic diseases are highly important in terms of the provision of treatment, prognosis, and genetic counselling. Although cortical malformations have been reported in patients with GLUT1 DS, the mechanism involved remains unclear, and this report highlights the potential relationship between cortical dysplasia and specific genotypes in GLUT1 DS. Further prospective observational and functional studies involving larger numbers of cases and centres are now needed.

1 | Introduction

The protein glucose transporter-1 (GLUT1) facilitates glucose diffusion across the blood–brain barrier by means of vascular endothelial cells. GLUT1 consists of 10 exons and is encoded by the 34 Kb *SLC2A1* gene on 1p34.2. Glucose is the brain's principal source of energy. Insufficient glucose transportation leads to the energy deficiency syndrome known as GLUT1 deficiency. GLUT1 deficiency syndrome (GLUT1 DS, OMIM 606777) was first described in 1991 (De Vivo et al. 1991). A pathogenic/likely pathogenic variant is determined in the *SLC2A1* gene in 93% of cases of GLUT1 DS and can cause a phenotype of variable severity (De Vivo et al. 1991).

GLUT1 DS affects all age groups, from infants to adolescents, with age-specific symptoms being observed. Classic GLUT1 DS is seen in 90% of cases and involves findings of early-onset seizures, complex movement disorder, predominantly ataxia and

dystonia, neurodevelopmental delay and acquired microcephaly. Nonclassic GLUT1 DS is observed in 10% of cases, in which seizures are not observed, and the condition involves a milder accompanying phenotype and paroxysmal dyskinesias (intermittent ataxia, choreoathetosis, dystonia and alternating hemiplegia) (Wang et al. 2002).

Cortical malformations are a series of complex and heterogeneous neurodevelopmental disorders that manifest with various macroscopic changes, including in brain structure, dimensions and morphology. They can also be associated with epilepsy, developmental delay and mental disability (Di Bella and Habibi 2023). Heterotopia is one of the cortical malformations that occur due to abnormal neuronal migration. Grey matter heterotopia is a cluster of normal neurons in abnormal locations, mainly due to impaired migration (Aronica and Mühlebner 2017). Heterotopia is identified at magnetic resonance imaging (MRI) in the form of conglomerations of grey matter in heterotopic locations and can be primarily categorized based on the morphology and location involved (Barkovich and Kuzniecky 2000). The causes of structural brain defects may be infectious, genetic/metabolic, environmental or multifactorial. A close association has been established between the in utero metabolic environment, including adaptation of energy, carbohydrate, lysosomal and amino acid metabolism and the development of the foetus and foetal organ maturation (BoAli et al. 2018). Case series and reports in the literature have investigated the relationship between brain malformation and inherited neurometabolic disorders. Bamforth reported a 17% relationship among such patients, and Prasad et al. reported one of 15% (Prasad et al. 2009; Bamforth et al. 1994).

Cranial imaging findings in cases of GLUT1 DS are variable. Cranial images in such cases may be accompanied by symptoms such as subcortical U fibre hyperintensity, the prominence of perivascular Virchow spaces and delayed myelination for age (Ismayilova et al. 2018; Wang et al. 2002). Confirmatory laboratory studies have observed low cerebrospinal fluid (CSF) glucose levels, low-normal CSF lactate levels and decreased glucose uptake by freshly prepared patient erythrocytes (Wang et al. 2005).

The purpose of this report is to describe rare genetic variants in two cases of GLUT1 DS with cortical dysplasia detected at MRI and exhibiting differing clinical presentations and to discuss the relationship between them.

2 | Methods

2.1 | Patients

Two cases presenting to the Balıkesir University Medical Faculty paediatric neurology clinic, Türkiye, between 01.08.2019 and 01.12.2024 due to seizures and inability to speak/numbness in the hands and arms, diagnosed as GLUT-1 DS, and with cortical dysplasia, were included.

The patients' files, MRI findings, physical examination findings and family pedigrees were evaluated. Informed consent was obtained from the parents. Permission for the study was granted by the local ethical committee (decision no. 2025/62 dated 04.02.2025).

2.2 | Genetic Testing

Genomic DNA was isolated automatically using a HiPurA Pre-filled Clinical Multipurpose Nucleic Acid Purification Kit with HIMEDIA InstaN Mag-96. Measurements for DNA concentration analysis were performed with Qubit (Thermo Fisher Scientific, USA). Whole exome sequencing was performed using a Roche KAPA HyperExome 96 rxn Kit with MGI DNBSEQ-G400. FastQ files were analysed with Genomize's SEQ platform version 8.7.0. The variants were classified according to American College of Medical Genetics (ACMG) 2015 Standards and Guidelines recommendations. Variants detected were confirmed using Sanger sequencing.

3 | Case Reports

3.1 | Case 1

A girl aged 11 years and 6 months was referred to us via the 112 emergency system due to a generalized tonic attack lasting 5 min, during which her eyes remained fixed on a single point and she lost consciousness. The patient's history revealed no previous trauma, infection, diarrhoea, vomiting or drug use. Her own and her family histories were unremarkable. At physical examination, she weighed 56 kg (90–95p) and was 163-cm tall (> 97p), with a head circumference of 55 cm (0 + 2 SD). Her arterial blood pressure was 110/70 (50p); S1+, S2+, heart sounds were rhythmical; and apart from a 1–2/6 systolic murmur, neurological and other system examinations were normal. Complete blood count, fingertip blood sugar, blood gas, biochemistry, TIT, CRP, ESR, TORCH, coagulation profile, metabolic screening tests (ammonia, lactate, urinary and blood amino acids, urinary organic acids, tandem mass spectrometry, and biotinidase), blood culture, urine culture, T4, TSH, anti-TPO, vitamin B12, vitamin D, ferritin and folic acid were all normal. Sleep and wake electroencephalography (EEG) performed in the interictal period was also normal. Cranial MRI revealed an appearance compatible with subependymal heterotopia at the level of the right lateral ventricle corpus (Figure 1). Ceftriaxone-acyclovir therapy was administered for 7 days due to suspicion of encephalitis (the family refused permission for lumbar puncture). Levetiracetam therapy was initiated at 20 mg/kg/day in two doses. At follow-up (1.5 years following the initiation of treatment), we learned that she experienced attacks involving an inability to walk and that these were triggered by hunger and intense exercise. These attacks lasted 5 to 30 min and were accompanied by numbness and weakness. In the light of the dyskinesia attacks triggered by paroxysmal exercise-induced dyskinesia and particularly since these symptoms emerged with hunger, whole exome sequencing was performed with a preliminary diagnosis of neurometabolic disease. A missense, heterozygous, likely pathogenic variant was detected in the *SLC2A1* gene. Segregation analysis identified this variant as de novo. The patient was diagnosed with GLUT1 DS and started on ketogenic diet therapy. The dyskinesia attacks subsequently resolved entirely. The patient's clinical characteristics are shown in Table 1.

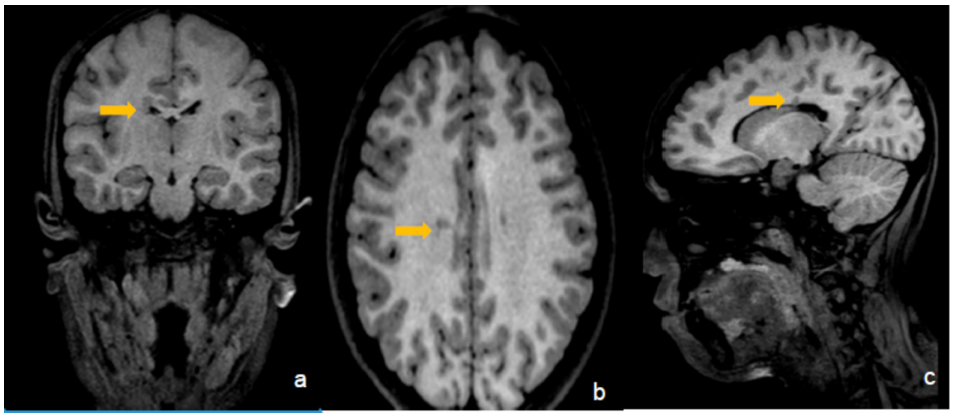


FIGURE 1 | (a–c): Coronal (1a), transverse (1b) and sagittal (1c) thin section 3D T1AG images from the same patient showing a focal lesion consistent with nodular heterotopia in the right parasagittal area, adjacent to the cingulate gyrus and lateral ventricle, showing an isointense signal with grey matter.

TABLE 1 | The cases' clinical and laboratory characteristics.

	Case 1	Case 2
Current age (years)	11 years 6 months	13 years
Gender	Female	Male
Gene (transcript)	*SLC2A1* (NM_006516.4)	*SLC2A1* (NM_006516.4)
Variant	c. 1208C > T	c. 278G > A
Exon	9	4
Zygosity	Heterozygous	Heterozygous
Microcephaly	–	–
Seizure (months) (onset)	11 years 6 months	–
Seizure type	Generalized tonic	–
Ambulatory	+	+
Expressive language	+	+
Cognitive delay	–	–
Ataxia	–	–
Other symptoms	Paroxysmal dyskinesia	–
MRI	Subependymal heterotopia	Cerebellar cortical dysplasia
EEG	Normal	Normal
Glucose CSF/blood	N/A	N/A

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalogram; MRI, magnetic resonance imaging; N/A, not applicable.

3.2 | Case 2

A 13-year-old boy was presented due to inability to speak for periods of half an hour and with numbness in the right upper extremity. During these times, he was conscious, with no contractions or incontinence. The patient's history was unremarkable, although his older brother had a history of valproic acid use due to febrile seizures. There was also no history of parental consanguinity. At physical examination, his body weight was 40 kg (15 p), height 158.6 cm (47 p), and head circumference 52.5 cm (−2.0 SDS). Detailed neurological and system examinations were normal. Complete blood count, fingertip blood sugar, blood gas, biochemistry, coagulation profile, metabolic screening tests were requested and his T4, TSH, anti-TPO, vitamin B12, vitamin D, ferritin and folic acid levels were measured. His vitamin D level was 13.4 mcg/L (30–70) and ferritin 8.1 mcg/L (23.9–336.2), and vitamin D and iron therapies were initiated. His wake and sleep EEG were evaluated as normal. Cranial MRI revealed grey matter atrophy and volume loss in the posterior–lateral aspect of the bilateral cerebellar hemispheres, prominence in the

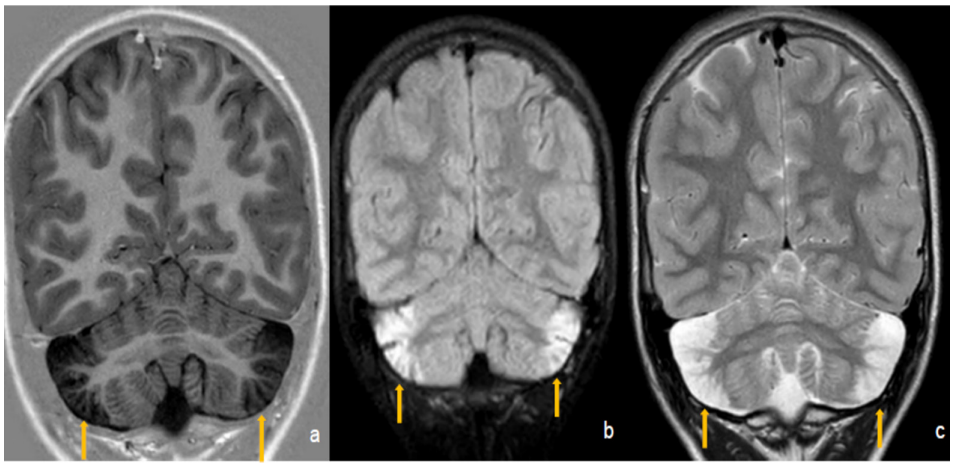


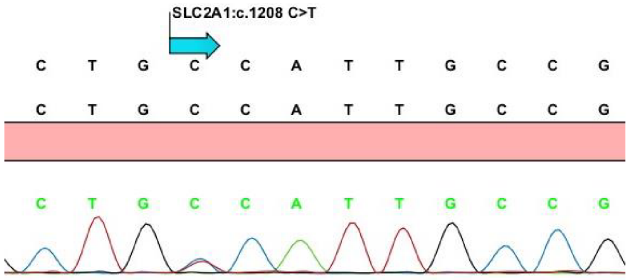
FIGURE 2 | (a–c): Coronal section T1AG (2a), Flair (2b) and T2AG (2c) images from the same patient. Figure 2a shows volume loss and atrophy in the grey matter in the posterior–lateral aspect of both cerebellar hemispheres, and Figure 2b,c shows a hyperintense signal in a symmetric configuration. The findings were consistent with cerebellar cortical dysplasia.

cerebellar folium and an appearance consistent with isolated cerebellar cortical dysplasia (Figure 2). The eye diseases department was consulted, but examination revealed no pathological findings. Whole abdomen ultrasonography and echocardiography examinations also revealed no pathology. Whole exome sequencing was performed with a preliminary diagnosis of neurometabolic disease. A heterozygous, likely pathogenic variant was detected in the *SLC2A1* gene. The case's clinical characteristics are shown in Table 1.

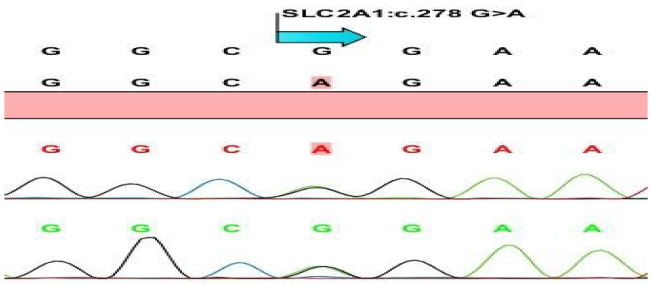
3.3 | Genetic Results

We detected two different pathogenic and likely pathogenic variants in *SLC2A1* (NM_006516.3) in patients from unrelated families. Patient 1 had a heterozygous c. 1208C > T variant. The variant allele fraction and sequencing depth were 0.3 and 113, respectively. The variant was classified as pathogenic according to ACMG criteria (ref: PMID: 25741868). This variant was not found in the gnomAD, ExAC, Turkish Variome population database. The locus was highly conserved in evolution: PhyloP100way 9.873; PhasCons100way 1. In silico predictors (DANN, CADD, and Revel) indicated a deleterious effect. The variant was reported in the ClinVar database (Variation ID: 2133173). Parental genetic analyses for the targeted variant were normal. Variants detected were confirmed using Sanger sequencing (Figure 3a).

Patient 2 exhibited a heterozygous likely c. 278G > A variant. The variant allele fraction and sequencing depth were 0.5 and 85, respectively. The variant was classified as likely pathogenic according to ACMG criteria (ref: PMID: 25741868). The variant exhibited an extremely low frequency in the gnomAD population database (0.000004156). The locus was conserved in evolution: PhyloP100way 4.9770; PhasCons100way 1. In silico predictors (DANN, Mutation Taster, MetaLR) indicated a deleterious effect. The variant was reported in the ClinVar database (Variation ID: 623684). Parental genetic analysis confirmed that the variant was maternally transmitted. Variants detected were confirmed using Sanger sequencing (Figure 3b).



a: Sanger sequencing confirmation of Case 1



b: Sanger sequencing confirmation of Case 2

FIGURE 3 | (a) Sanger sequencing confirmation of Case 1. (b) Sanger sequencing confirmation of Case 2.

4 | Discussion

The clinical manifestation of GLUT1 DS can range from mild motor dysfunction to severe and widespread neurological disability. It represents a basic characteristic of epilepsy and affects 80%–90% of patients. Seizures generally commence in the first year of life but can also rarely be seen in adulthood. Mixed type seizures are observed in approximately 70% of patients, most commonly in the form of generalized tonic clonic and absence

seizures. EEG findings are highly variable, and there is no typical EEG pattern (Gras et al. 2014). EEG in the interictal period in GLUT1 DS is generally normal at all ages (Vaudano et al. 2016). Case 1 in this report also experienced generalized tonic clonic seizure, while both cases' EEG findings were normal.

Psychomotor retardation, generally mild, is seen in 80%–98% of patients with GLUT-1 DS. The syndrome has also rarely been detected in children with normal psychomotor development and adults with normal cognitive functions (Ito et al. 2015; Leen et al. 2010; Pons et al. 2010). Both our patients exhibited normal neuromotor development and good academic performance.

Normal cranial imaging findings in cases including GLUT 1 DS have been reported to be accompanied by minor nonspecific abnormal findings (Wang et al. 2005). Levy et al. detected significant MRI abnormalities such as white/grey matter anomalies, a thin corpus callosum and expanded ventricles in a case of GLUT1 DS with the largest deletion (Levy et al. 2010). In terms of cranial imaging of previous cases of GLUT1 DS in the literature, Hewson et al. observed focal or diffuse cortical dysplasia/heterotopia in 5%, while Qingqing et al. reported accompanying findings of cortical dysplasia in 8% (Hewson et al. 2018; Hu et al. 2021). In the current report, an appearance consistent with subependymal heterotopia was observed in Case 1 and with cerebellar cortical dysplasia in Case 2. Approximately 81%–89% of cases are diagnosed using sequencing analysis and 11%–14% using deletion/duplication analysis (Wang et al. 2002). The only case in the literature in which a heterotopia phenotype was described and with a reported molecular aetiology was published by Bourque et al. (2021). Although heterotopia is rarely reported in GLUT1 DS, the relationship between a heterotopia finding and variant remains unclear, and no genotype/phenotype correlation has been identified.

GLUT1 is selectively expressed in brain capillaries, astroglia, erythrocytes and blood–brain barrier endothelial cells (Pardridge et al. 1990). Blood–brain barrier dysfunction is known to play a role both in the emergence of seizures and in the subsequent conversion to epilepsy (Van Vliet et al. 2007; Weissberg et al. 2011). A previous animal study reported a persistent decrease in GLUT-1 and glucose deficiency before and during second-hit-induced epileptogenesis in the brains of rats with cortical dysplasia (Ghosh et al. 2022). Glucose is the principal energy source of the brain, and GLUT1 facilitates glucose transportation across the plasma membranes of blood–brain barrier endothelial cells (Jha and Morrison 2018). A dysfunctional glucose transport mechanism in the blood–brain barrier may therefore affect glucose transportation to the brain and subsequent metabolic activity in rats with cortical dysplasia (Huang et al. 2015). The metabolic and developmental pathways are closely related and also react with one another. In contrast to these findings shown in animal experiments, the reason for the cortical dysplasia observed in patients with GLUT1 DS is unclear. Whether this is incidental, represents a cause and effect relationship or derives from an energy metabolism defect during migration abnormalities is not yet known.

The limitations of this study include the fact that lumbar puncture could not be performed since the families refused permission, that CSF glucose could not be correlated with clinical severity and that functional analyses could not be conducted.

In conclusion, the careful evaluation of patients with structural brain damage and determination of the molecular aetiology of underlying inherited metabolic diseases are highly important in terms of prognosis, appropriate treatment and genetic counselling. In particular, GLUT1 DS should also be considered in the differential diagnosis of patients with metabolic diseases with heterotopia, such as Zellweger syndrome, carnitine palmitoyltransferase II deficiency, glutaric aciduria type 2, Menkes disease, fumarase deficiency and pyruvate carboxylase deficiency (BoAli et al. 2018). Although cortical malformations have been reported in patients with GLUT1 DS, the mechanism involved remains unclear, and this report was intended to emphasize the relationship with the genotype. SLC2A1 gene variants may play a role in cortical development by disrupting glucose metabolism, which is critical for neurogenesis and neuronal migration. Further prospective observational and functional studies involving a larger number of cases and centres are now needed.

Author Contributions

H.A., H.B, Z.E. and A.A. wrote the main part of the manuscript. H.B and Z.E performed and interpreted the genetic tests. H.A., H.B., Z.E. and A.A. collected and interpreted the clinical data. Both authors critically revised and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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