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Case Report / Olgu Sunumu

Glucose Transporter Type 1 Deficiency Syndrome: A Single-Center Case Series

Glukoz Transport Tip 1 Eksikliği Sendromu: Tek Merkez Olgu Serisi

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Abstract

Glucose transporter type 1 deficiency syndrome is a neurometabolic encephalopathy characterized by movement disorders, intractable seizures, and acquired microcephaly. Two girls and a boy between the ages of 3 and 15 years were included in this study. The main clinical manifestations were seizure, ataxia, global developmental delay, and acquired microcephaly. The most common electroencephalographic finding was interictal focal or generalized epileptiform discharges. The cerebrospinal fluid to blood glucose ratio was determined to be low (0.35 and 0.40). Two cases had heterozygous *de novo* mutations and one had microdeletion of SLC2A1. All cases were treated with a ketogenic diet (KD) and were seizure-free in the sixth month of the diet. KD also improved ataxic gait, language skills, and behavioral disturbances. Inconsistency was demonstrated between electroencephalography findings and seizure semiologies detected in patients with GLUT1DS, and KD was found to be most effective for seizures and less effective for ataxia, language skills, and behavioral disturbances.

Keywords: Glucose transporter type 1 deficiency syndrome, ataxia, *SLC2A1*, ketogenic diet

Öz

Glukoz transport tip 1 eksikliği sendromu hareket bozuklukları, dirençli nöbetler ve edinilmiş mikrosefali ile karakterize bir nörometabolik ensefalopatidir. Çalışmaya 3 ila 15 yaşları arasında iki kız ve bir erkek çocuk dahil edildi. Başlıca klinik belirtiler nöbet, ataksi, global gelişimsel gecikme ve edinilmiş mikrosefaliydi. En sık görülen elektroensefalografik bulgu interiktal fokal veya jeneralize epileptiform deşarjlardı. Beyin omurilik sıvısı/kan şekeri oranının düşük olduğu belirlendi (0,35 ve 0,40). İki olguda heterozigot *de novo* mutasyon ve bir olguda *SLC2A1* geninde mikrodelesyon saptandı. Tüm olgular ketojenik diyet (KD) ile tedavi edildi ve diyetin altıncı ayında nöbetsizlerdi. KD ayrıca ataksik yürüyüş, dil becerileri ve davranış bozukluklarını da iyileştirdi. Glukoz transport tip 1 eksikliği sendromunda elektroensefalografi bulguları ile nöbet semiyolojileri arasında tutarsızlık tespit edilebileceğini, KD'nin nöbetler üzerinde belirgin etkili ve ataksi, dil becerileri ve davranış bozuklukları üzerinde ise daha az etkili olduğunu gösterdik.

Anahtar Kelimeler: Glukoz transport tip 1 eksikliği sendromu, ataksi, *SLC2A1*, ketojenik diyet

Introduction

Glucose transporter type 1 deficiency syndrome (GLUT1DS) is a rare neurometabolic encephalopathy, which results in impaired glucose transportation across the blood-brain barrier. The classic phenotype of GLUT1DS manifestations is intractable seizures, developmental delay, episodic movement disorders, and acquired microcephaly (1,2). GLUT1DS causes wide spectrum clinical phenotypes from intractable seizures to episodic movement disorders. The gold standard treatment is the ketogenic diet (KD), wherein derived ketone bodies cross the blood–brain barrier and provide an alternative source of energy for brain metabolism (1,2).

This study aimed to retrospectively describe the clinical features, laboratory findings, treatments, and outcomes of patients with GLUT1DS in our department.

Case Reports

Demographic and clinical features, laboratory and imaging findings, treatment, and outcome of three patients with

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GLUT1DS admitted at our department between 2015 and 2020 were retrospectively reviewed.

Cranial magnetic resonance imaging (MRI), electroencephalography (EEG), and genetic analysis were performed in all cases. Lumbar puncture (LP) was performed in two cases after a 4-hour fasting period. Cerebrospinal fluid (CSF) and blood glucose were simultaneously measured; blood glucose was measured just before the procedure to avoid stress hyperglycemia. The requirements of all cases were planned with the dietician (FI). No liquid and calorie restrictions were made. All cases received multivitamin and mineral, calcium, vitamin D, and omega-3 supplements.

Two girls and a boy between the ages of 3 and 15 years were included in the study. The age of onset symptoms ranged from 3 to 6 months. The seizure was the first presenting symptom in all cases. Five seizure types were defined as follows: absence (n=3), generalized tonic-clonic (n=2), generalized tonic (n=2), myoclonic-atonic (n=1), and myoclonic (n=1). Physical and neurological examinations revealed a variable combination of ataxia, spasticity, acquired microcephaly, developmental delay, pyramidal signs, facial dysmorphism, stereotyped hand movements, gaze palsy, oculomotor apraxia, hypotonia, and muscle weakness. The EEGs demonstrated interictal focal or generalized epileptiform discharges (n=3) and generalized background slowing (n=2). Biochemical tests, metabolic tests, and cranial MRI findings were normal in all cases. LP was performed in two cases after a 4-hour fasting period, and the CSF glucose levels were determined to be low (30 and 38 mg/dl). The CSF to blood glucose ratios were low (0.35 and 0.40), with normal CSF lactate levels. Two patients had heterozygous *de novo* mutation [case 1: c.389G>A (p.G130D) (p.Gly130Asp), which is a novel heterozygous mutation and case 3: c.734A>C (p.K245T) (p.Lys245Thr)] and one (case 2) had microdeletion 1p34.2 (15.6 kb) of *SLC2A1*. All cases were treated with KD, which was well tolerated. They were seizure-free in the sixth month of diet. The KD slightly improved the ataxic gait (n=3), language skills (n=2), and behavioral disturbances (n=1). Demographic, clinical, laboratory and imaging findings, treatments, and outcome of cases were summarized in Table 1.

Discussion

GLUT1DS is a neurometabolic encephalopathy, classically characterized by complex movement disorders, drug-resistant epilepsy, developmental delay, and acquired microcephaly (1,2). Seizures are usually the most common first symptom, occurring in infancy or early childhood. In a large cohort study, Pong et al. (3) revealed that 90% of 87 patients with GLUT1DS had epilepsy, with an average onset at 8 months of age. Likewise, all cases of our study had epilepsy, with seizure onset between ages 3 to 6 months.

The clinical spectrum of GLUT1DS was broadened with recent studies. Some patients showed mild clinical findings and were asymptomatic between episodes, others showed severe clinical findings, such as global developmental delay and intractable seizures (2). In a large case series, Leen et al. (1) suggested that missense mutations are associated with mild clinical phenotypes. In contrast, large-scale deletions, non-sense, frameshift, and splice-site mutations are associated with more severe clinical phenotypes. Similarly, in our series, case 2 with the microdeletion of *SLC2A1* had more severe clinical findings.

Ataxia, spasticity, paroxysmal dystonia, choreoathetosis, exercise-induced dyskinesia, tremor, and myoclonus are the main types of movement disorders in GLUT1DS (1,4). In our series, all cases had ataxia (two had intermittent ataxia facilitated by exercise and fasting, one had persistent ataxia) and one had spasticity. Persistent ataxia (in case 2), oculomotor apraxia, and stereotyped hand movements (in case 3), which are rare findings in GLUT1DS, were detected in our series (2,4).

The main types of epilepsy in GLUT1DS are generalized tonic-clonic, absence, complex partial, myoclonic, and myoclonic-atonic (3). Various seizure types were defined in our series including absence, generalized tonic-clonic, generalized tonic, myoclonic-atonic, and myoclonic. The GLUT1DS electroencephalographic findings were variable and fluctuated from one form to another at different times with or without fasting (5,6). In the present study, several EEG findings including focal or generalized epileptiform discharges and/or generalized background slowing were found. Being aware of the limited power due to the number of cases, we determined that there was inconsistency between EEG findings and seizure semiologies. However, our study includes only three cases; thus inconsistency is investigated in larger groups. Moreover, in the literature, Brockmann (2) defined a "carbohydrate-responsive" phenotype in which seizures and movement disorders are improved after carbohydrate intake, together with a marked EEG improvement. These observations were confirmed by other authors (5,6).

One of the most important laboratory tests is the CSF to blood glucose ratio after a 4-6 hours fasting period (7). In the present study, LP was performed in two cases and CSF to blood glucose ratio was low. In a large case series, Leen et al. (1) revealed that the CSF to blood glucose ratio correlated with the phenotype, which suggested that the degree of impairment of glucose transport into the brain is an indicator of symptom severity in GLUT1DS. In contrast, low CSF to blood glucose ratio was demonstrated not to be always associated with a more severe phenotype in some individual patients. Moreover, a study by Hully et al. (8) found similar findings. In the present study, the CSF to blood glucose ratio was lower in case 1 than that of case 2, but the clinical findings were milder in case 1. Therefore, CSF to blood glucose ratio is not always associated with more severe clinical symptoms.

GLUT1DS diagnosis should be confirmed by gene mutation analysis. Gene mutations are sporadic, autosomal dominant, or autosomal recessive (1,2). GLUT1DS are part of microdeletion syndromes involving *SLC2A1* (1,9). Case 1 had novel heterozygous *de novo* mutation (c.389G>A), case 2 microdeletion on 1p34.2, and case 3 heterozygous *de novo* mutation (c.734A>C) previously reported by Çolak et al. (10).

Ketone bodies produced by a high-fat and low carbohydrate diet provide an alternative fuel of glucose in the brain, which allows bypassing the metabolic defect. KD is the gold standard therapy in patients with GLUT1DS (11). In our series, KD showed a remarkable improvement in seizures and milder improvement in non-epileptic conditions such as ataxic gait, language skills, and behavioral disturbances but with fewer efficacies in cognitive disturbances.

In conclusion, a case series of patients with GLUT1DS presenting with heterogenic phenotypes and genotypes was described. In our series, CSF to blood glucose ratio was demonstrated not to be

Table 1. Demographic, clinical, laboratory and imaging findings, treatment, and outcome of GLUT1DS cases

Case no	Age at diagnosis/ sex	First symptom	Age at first seizure (month)	Clinical and examination findings	Seizure type	Cranial MRI	EEG	CSF to blood glucose ratio/ CSF lactate	Genetic analysis	Treatment (all AEDs used so far)	KD type	Outcome
1	3 years/F	Seizure	5	Seizure, mild global developmental delay, ataxia, acquired microcephaly	Absence, myoclonic-atonic, generalized tonic-clonic	Normal	Rare high amplitude spike and spike-wave discharges in bilateral frontal regions	0.35/ normal	A novel heterozygous *de novo* mutation in SLC2A1; c.389G>A (p.G130D) (p.Gly130Asp).	Phenobarbital, levetiracetam, valproic acid, pyridoxine	3:1	Seizure-free, antiepileptic treatment was stopped, slightly improved language skills and ataxic gait
2	15 years/M	Seizure	6	Seizure, severe global developmental delay, ataxia, acquired microcephaly, spasticity and pyramidal signs in lower limbs, facial dysmorphism	Absence, generalized tonic, generalized tonic-clonic	Normal	High amplitude spike and spike-wave discharges in left parieto-occipital regions and generalized background slowing	0.40/ normal	Microdeletion on 1p34.2 (15.6 kb) in array-CGH	Carbamazepine, valproic acid, clonazepam	3:1	Seizure-free, the number of antiepileptic drugs was reduced, slightly improved language skills, behavioral disturbances, and spastic ataxic gait
3	4 years and 4 months/F	Seizure	3	Seizure, moderate global developmental delay, ataxia, acquired microcephaly, stereotyped hand movements, gaze palsy, oculomotor apraxia, mild truncal hypotonia, muscle weakness	Absence, myoclonic, generalized tonic	Normal	Rare generalized high amplitude spike and spike-wave discharges and mild generalized background slowing	ND	Heterozygous *de novo* mutation in SLC2A1 gene; c.734A>C (p.K245T) (p.Lys245Thr)	Phenobarbital, levetiracetam, pyridoxine, vigabatrin, ACTH, topiramate, valproic acid, carbamazepine, clobazam	2:1	Seizure-free, the number of antiepileptic drugs was reduced, slightly improved ataxic gait

F: Female, M: Male, MRI: Magnetic resonance imaging, EEG: Electroencephalography, CSF: Cerebrospinal fluid, ND: Not documented, ACTH: Adrenocorticotropic hormone, AED: Antiepileptic drug, KD: Ketogenic diet

associated with clinical severity, with inconsistency between EEG findings and seizure semiologies in patients with GLUT1DS, and KD was found to be most effective on seizures and less effective on ataxia, language skills, and behavioral disturbances. Further case series on GLUT1DS are required to expand the phenotypic-genotypic spectrum and determine the effect of KD on long-term outcomes.

Ethics

Informed Consent: Informed consent was obtained from the parents of the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.I., Concept: M.Y., D.Y., M.T., Design: M.Y., Ö.B., M.T., Data Collection or Processing: M.Y., F.I., D.Y., Analysis or Interpretation: M.Y., D.Y., M.T., Literature Search: M.Y., Ö.B., F.I., Writing: M.Y., Ö.B., F.I.

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