CASE REPORTS

UDC: 616.8-053.2
https://doi.org/10.2298/VSP170406120I

GLUT1 deficiency syndrome: a case report with a novel *SLC2A1* mutation

GLUT1 sindrom deficijencije – prikaz bolesnika sa mutacijom u *SLC2A1* genu

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Abstract

Introduction. GLUT1 deficiency syndrome (GLUT1 DS, *OMIM 606777*) is a metabolic brain disorder caused by mutations in *SLC2A1* gene (chromosome 1) encoding glucose transporter type 1 located on blood-brain membrane. The "classic" phenotype in children includes early onset generalized farmacoresistant epilepsy, developmental delay, complex movement disorders and acquired microcephaly. However, there are milder phenotypes without epilepsy which could be seen in older children. The ketogenic diet is a treatment of choice. **Case report.** We present a four-year-old female patient with farmacoresistant generalized epilepsy, paroxysmal dystonic posturing, ataxia, hypotonia, developmental delay (motor, attention and speech disturbances), and microcephaly. The genetic testing revealed a novel point mutation at c.156T > A (p.Y52X) in exon 3 of *SLC2A1* gene. The patient responded excellent on ketogenic diet. **Conclusion.** GLUT1 DS is treatable, and likely to be under-diagnosed neurological disorder. The ketogenic diet is resulting in good control of seizures in the patients, and it has certain benefit for the neurodevelopmental disability.

Key words:
glut1 deficiency syndrome; diagnosis; diet ketogenic; treatment outcome.

Apstrakt

Uvod. GLUT1 sindrom deficijencije (GLUT1 DS, *OMIM 606777*) je metaboličko oboljenje mozga uzrokovano mutacijom u *SLC2A1* genu (hromozom 1) koji kodira transporter glukoze tip 1 lokalizovan na krvno-moždanoj barijeri. "Klasični" fenotip kod dece uključuje ranu pojavu generalizovane farmakorezistentne epilepsije, usporen psihomotorni razvoj, poremećaje pokreta i stečenu mikrocefaliju. Međutim, blaži fenotipovi bez pojave epilepsije mogu se videti i u kasnijem uzrastu. Ketogena dijeta je terapija izbora. **Prikaz bolesnika.** U radu je prikazana devojčica, uzrasta četiri godine sa farmakorezistentnom generalizovanom epilepsijom, paroksizmalnim distonijama, ataksijom, hipotonijom, usporenim razvojem (poremećajima motorike, pažnje i govora) i mikrocefalijom. Genetsko testiranje je otkrilo novu tačkastu mutaciju u c.156T > A (p.Y52X) na egzonu 3 *SLC2A1* gena. Kod bolesnice je primećeno poboljšanje u kliničkom nalazu na primenu ketogene dijete. **Zaključak.** GLUT1 DS je lečiva neurološka bolest, koja je verovatno nedovoljno prepoznata. Ketogena dijeta dovodi do povoljne kontrole napada kod dece, a doprinosi izvesnom poboljšanju u neurološkom nalazu.

Ključne reči:
sindrom deficijencije glut1; dijagnoza; dijeta, ketogena; lečenje, ishod.

Introduction

GLUT1 deficiency syndrome (GLUT1 DS, *OMIM 606777*) is a metabolic brain disorder arising from mutations in the neuronal glucose transporter GLUT1 (now designed *SLC2A1*) at short arm of chromosome 1 (1p35–31.3)[1]. GLUT1 located at the blood brain barrier is the main vehicle for glucose transport into the brain. The disease is caused by impaired D-glucose transport across the blood brain barrier, exposing the brain to the risk of energy failure.

The syndrome was first described by De Vivo et al.[2] (1991) in two children with early-onset epilepsy, developmental delay and acquired microcephaly. They had a low cerebrospinal fluid concentration of glucose and normal plasma glucose concentration. GLUT1 DS is characterized by infantile onset refractory epilepsy, cognitive and motor develop-

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mental delay, and mixed motor disorders including spasticity, ataxia and dystonia [1]. Affected infants have neurodevelopmental impairment of variable severity and acquired microcephaly. Some patients have milder phenotypes and others have more severe with permanent neurological deficits. The cardinal biochemical feature is a decreased ratio of cerebrospinal fluid glucose relative to the plasma glucose concentration [3].

GLUT1 DS is caused by haploinsufficiency of *SLC2A1* gene due to a *de novo* heterozygous mutation in a majority (90%) of cases. About 10% of patients have autosomal dominant inheritance and one affected parent, and only a few cases have autosomal recessive [1, 3].

GLUT1 DS is a treatable disorder and a lot of patients, especially those with a mild phenotype, are likely to be underdiagnosed [1–3]. The ketogenic diet is the mainstay of treatment, resulting in good control of seizures in most patients and it has certain benefit for the neurodevelopmental disability.

Case report

We presented a four-year-old female infant born at term by vaginal vertex delivery. There were no complications during pregnancy. Birth weight was 3 300 g and the 5-minutes Apgar score was 10. The physical examination at birth was without signs of abnormalities. Her parents were nonconsanguineous and healthy. Family history was unremarkable with no history of developmental problems, learning deficits, birth defects or genetic syndromes.

At the age of 6 months, the neurological examination revealed microcephaly, mild hypotonia, reduced motor activity, brisk deep tendon reflexes and developmental delay. The girl started to sit without support from the age of one year and to walk on a wide base, with support and with spastic-ataxic component from the age of two and a half years. She never attained the ability to walk. Speech development was also delayed. She had dysarthria with difficult understanding and very poor expressive speech. She was able to put words into phrases from the age of three years and her developmental quotient was 60. She had moderate intellectual impairment. Intensive physical and speech rehabilitation was performed.

First seizures were noticed starting from the age of 18 months with brief episodes of unresponsiveness, eye movements, head bobbing and hypotonia. The interictal electroencephalography (EEG) recording showed generalized spike and wave discharges with a frequency of 2.5–4 Hz. Antiepileptic therapy was given (valproate 30 mg/kg) and it resulted in exacerbation of seizures, so the drug was excluded. The seizures were also resistant to antiepileptic drugs clonazepam, clobasam and lamotrigine. Atypical absence seizures as the most common type of seizures were noticed at the age of three years and ethosuximide was introduced. The girl responded readily and better control of seizures was achieved. Later, levetiracetam was added with satisfactory results. The magnetic resonance imaging (MRI) of the brain done twice at the age of two and three years was normal. Metabolic investigations were within normal limits.

The genetic testing encompassed array comparative genomic hybridization (aCGH) and *SLC2A1* gene sequencing. Normal result was obtained using aCGH, showing only one polymorphic copy number variant (loss of approx. 1.3 Mb at 15q11.2). Sanger sequencing of *SLC2A1* gene disclosed variant c.156T > A (p.Y52X) in the exon 3 of the gene. This variant was not reported in the databases of The Exome Aggregation Consortium (ExAC), 1000 Genomes, and Human Gene Mutation Database (HGMD). The prediction analysis using the MutationTaster software indicated pathogenicity of the variant.

After the diagnosis of GLUT1 DS had been confirmed, the ketogenic diet (4 : 1 ratio) was introduced. Complete control of seizures was achieved. The girl is now 4 years old and shows delay in psychomotor development. She has microcephaly, abnormal gait (spastic-ataxic) and speech delay. She does not have seizures at all.

Discussion

Most patients with GLUT1 DS have perinatal history without complications, like in our reported patient [3]. The neurological findings in the "classic" GLUT1 DS include epileptic encephalopathy, complex movement disorders (ataxia, dystonia, spasticity) and developmental delay including cognitive deficits. It also includes hypotonia and acquired microcephaly. Our patient showed all these characteristic features. In the literature, the average age for confirming diagnosis is 5 years [4] and in our patient it was 4 years.

Recently, the "non-classic" clinical features of GLUT1 DS have included familiar and sporadic paroxysmal exercise-induced dyskinesia with or without epilepsy [5–7]. It could also include varying degrees of cognitive deficits, dysarthria, dysfluency and expressive language deficits. Awareness of the broad range of potential clinical phenotypes associated with GLUT1 DS facilitates diagnosis. Post et al. [8] listed the most frequent movement disorders as gait disturbances, dystonia, chorea, non-epileptic paroxysmal events, etc. Most patients have several types of movement disorders. Additionally, the syndrome of paroxysmal choreoathetosis with spasticity (DYT9), and paroxysmal exertional dyskinesia (DYT18) were also included as a part of clinical variability of GLUT1 DS [9, 10].

The onset of seizures in GLUT1 DS occurs between 4 weeks and 18 months of age and in our patient the onset was at the age of 18 months. They include all seizure types (focal, generalized, absence and myoclonic) and are resistant to antiepileptic drugs [3, 11]. In our patient, atypical absence seizures were observed to be resistant to different drugs. They showed, however, good clinical response to etosuximide and levetiracetam. The EEG findings in our patient was also typical for this syndrome (generalized 2.5–4 Hz spike and wave discharges), while the neuroimaging findings as normal [1]. In fact, the conventional anatomic neuroimaging with computed tomography (CT) or the MRI is typically normal in the patients with GLUT1 DS, whereas the metabolic imaging with ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) reveals a distinctive pattern of hypometabolism in the thalami and mesial temporal regions. It suggests impaired function of thalamo-cortical network as an important factor in epileptogenesis [12].

Certain antiepileptic drugs, like valproate, have the potential to exacerbate seizures and that happened to our patient. It is confirmed that valproate can significantly inhibit the GLUT1 function and glucose transport resulting in the increased seizure activity in the patient with GLUT1 DS. Therefore, it is important to be careful with the use of valproate in the patient with compromised function of GLUT1 [1, 13].

The ketogenic diet (high-fat, carbohydrate-restricted) plays an indispensible role in the treatment of GLUT1 DS. It mimics the metabolic state of fasting, providing ketone bodies, derived from the hepatic metabolism of fatty acid, as an alternative fuel source for the brain. Therefore, the ketogenic diet is a proven therapy for the treatment of seizures and other clinical features of the syndrome. This treatment in our patient resulted in subsequent improvement in her neurological status (gait, ataxia, spasticity) as well as cessation of seizures [14–16].

Our patient fulfilled the criteria for the "classic" phenotype of GLUT1 DS: epilepsy, developmental delay, cognitive deficit, microcephalia, hypotonia, spasticity and a complex movement disorders (ataxia, dystonia). The diagnosis in our patient was confirmed by identification of pathogenic nucleotide substitution in the exon 3 of the *SLC2A1* gene.

The phenotype-genotype correlation is not well-established. The relationship between clinical and genetic characteristics is analyzed in one study [17]. Sporadic cases with *SLC2A1 de novo* mutation (direct gene sequencing revealed missense, nonsense and splice site mutation) had a more severe phenotype than familiar cases (all patients presented with missense mutation). Sporadic cases had more profound cognitive disability, more severe form of epilepsy and neurologic deficits. The milder phenotype was observed in familiar cases in the form of "benign" epilepsy and slight movement disorder. Another study presented that missense mutations more frequently showed "mild" phenotype [18], which, of course, could be observed in a variety of other genetic disorders. However, the patients with the same mutation could show phenotypic variety, suggesting that other genes or other proteins are involved in glucose transport, pathophysiology of the disease and phenotype. It raises the unsolved question on the real incidence of GLUT1 DS, treatment with ketogenic diet in milder forms of disease and concerns about genetic counseling [19, 20].

Conclusion

We presented the patient with GLUT1 DS, novel causative *SCL2A1* gene variant and effective treatment with ketogenic diet. Although presentation was rather typical, diagnosis was confirmed at the age of 4 years which is in concordance with reports from other centers. It is well-established that early initiation of the ketogenic diet results in better seizure control and improves the neurologic outcome. One solution could be an employment of massive parallel gene sequencing in an early course of infantile seizures, which could provide timely diagnosis in a substantial proportion of patients.

Acknowledgements

This work was supported by the Serbian Ministry of Education, Science and Technological Development (Grant ON175091).

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Received on April 06, 2017.
Accepted on July 07, 2017.
Online First September, 2017.