ACCEPTED MANUSCRIPT

Accepted manuscripts are the articles in press that have been peer reviewed and accepted for publication by the Editorial Board of the Vojnosanitetski Pregled. They have not yet been copy edited and/or formatted in the publication house style, and the text could still be changed before final publication.

Although accepted manuscripts do not yet have all bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: article title, the author(s), publication (year), the DOI.

Please cite this article: GLUT1 DEFICIENCY SYNDROME: A CASE REPORT WITH A NOVEL SLC2A1 MUTATION

Authors: Nikola Ivančević*, Nataša Cerovac†, Blažo Nikolić‡, Goran Čuturilo§, Ana Marjanović‖, Marija Branković¶, Ivana Novaković**; Vojnosanitetski pregled (2017); Online First September, 2017.

UDC:

DOI: https://doi.org/10.2298/VSP170406120I

When the final article is assigned to volumes/issues of the Journal, the Article in Press version will be removed and the final version appear in the associated published volumes/issues of the Journal. The date the article was made available online first will be carried over.
GLUT1 deficiency syndrome: a case report with a novel SLC2A1 mutation

Nikola Ivančević*, Nataša Cerovac†, Blažo Nikolić‡, Goran Čuturilo§, Ana Marjanović‖, Marija Branković¶, Ivana Novaković**

* Clinic of Neurology and Psychiatry for Children and Youth, Faculty of Medicine, University of Belgrade, Serbia
† Clinic of Neurology and Psychiatry for Children and Youth, Faculty of Medicine, University of Belgrade, Serbia
‡ Clinic of Neurology and Psychiatry for Children and Youth, Faculty of Medicine, University of Belgrade, Serbia
§ University Children’s Hospital, Faculty of Medicine, University of Belgrade, Serbia
‖ Clinic of Neurology, Faculty of Medicine, University of Belgrade, Serbia
¶ Clinic of Neurology, Faculty of Medicine, University of Belgrade, Serbia
** Clinic of Neurology, Faculty of Medicine, University of Belgrade, Serbia
Sažetak

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 slučaja: prikazujemo devojčicu uzrasta 4 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. Pacijent je pokazao 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: GLUT1 DS, fenotip, genotip, ketogena dijeta

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 years old female patient with farmacoresistant generalized epilepsy, paroxysmal dystonic posturing, ataxia, hypotonia, developmental delay (motor, attention and speech disturbances), and microcephaly. Genetic testing revealed a novel point mutation at c.156T>A (p.Y52X) in exon 3 of SLC2A1 gene. 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 DS, phenotype, genotype, ketogenic diet

**Introduction**

GLUT1 deficiency syndrome (GLUT1 DS, *OMIM 606777*) is a metabolic brain disorder arising from mutations in the neuronal glucose transporter GLUT1 (now designated *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 and associates (1991) in two children with early-onset epilepsy, developmental delay and acquired microcephaly (2). 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 developmental 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 majority (90 %) of cases. About 10 % of patients have autosomal dominant inheritance and one affected parent, and only a few cases 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 under-diagnosed (1, 2, 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 3300 g and 5-minutes Apgar score was 10. 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 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 has 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 has been 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. 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. 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.

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 has not been reported in databases The Exome Aggregation Consortium (ExAC),
1000 Genomes, and Human Gene Mutation Database (HGMD). Prediction analysis using 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). 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, 6, 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. listed the most frequent movement disorders as gait disturbances, dystonia, chorea, non-epileptic paroxysmal events etc (8). 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 GLUT1DS 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. EEG findings in our patient was also typical for this syndrome (generalized 2.5 – 4 Hz spike and wave discharges), while neuroimaging findings as normal (1). In fact, conventional anatomic neuroimaging with CT or MRI is typically normal in patients with GLUT1 DS, whereas 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 in our patient. It is confirmed that valproate can significantly inhibit the GLUT1 function and glucose transport resulting in increased seizure activity in patient with GLUT1 DS. Therefore, it is important to be careful with the use of valproate in 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 neurological status (gait, ataxia, spasticity) as well as cessation of seizures (14, 15, 16).

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

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 had 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 showed that missense mutations more frequently showed “mild” phenotype (18), which of course could be observed in a variety of other genetic disorders. However, 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 other centers’ reports. It is well established that early initiation of the ketogenic diet results in better seizure control and improves neurologic outcome. One solution could be employment of massive parallel gene sequencing in an early course of infantile seizures, which could provide timely diagnosis in a substantial proportion of patients.

**Acknowledgments:**

This work was supported by the Serbian Ministry of Science, Technology and Development

Grant ON175091

**REFERENCES**


2. **De Vivo DC, Trifiletti RR, Jacobson RI, Ronen GM, Behmand RA, Harik SI.**


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