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Case Report

Novel mutation in a patient with late onset GLUT1 deficiency syndrome

Sandra Juozapaite [a,*], Ruta Praninskiene [a,b], Birute Burnyte [c,d], Laima Ambrozaityte [c,d], Birute Skerliene [a,b]

[a] *Children's Hospital, Affiliate of Vilnius University Hospital Santariskiu Clinics, Santariskiu st. 7, Vilnius 08406, Lithuania*
[b] *Clinic of Children's Diseases, Faculty of Medicine, Vilnius University, M. K. Ciurlionio st. 21, Vilnius 03101, Lithuania*
[c] *Department of Human and Medical Genetics, Faculty of Medicine, Vilnius University, M. K. Ciurlionio st. 21, Vilnius 03101, Lithuania*
[d] *Center for Medical Genetics, Vilnius University Hospital Santariskiu Clinics, Santariskiu st. 2, Vilnius 08661, Lithuania*

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Abstract

Glucose transporter 1 deficiency syndrome (GLUT1-DS) is an inborn error of metabolism caused by impaired glucose transport through blood brain barrier due to mutation in *SLC2A1* gene, encoding transporter protein. Clinical spectrum includes various signs and symptoms, ranging from severe epileptic encephalopathy to movement disorders. The diagnosis of GLUT1-DS requires hypoglycorrhachia in the presence of normoglycaemia with a reduced cerebrospinal fluid (CSF):plasma glucose ratio. The absence of pathogenic mutation in *SLC2A1* gene does not exclude the diagnosis. This case report describes a patient with late onset GLUT1-DS with a novel sporadic mutation c.539T>A, p.Met180Lys in exon 5 of the *SLC2A1* gene. The dominating clinical features were epilepsy and paroxysmal dyskinesias provoked by infection, emotional stress and fasting. The ictal EEG was characterized by generalized paroxysmal 3–3.5 Hz spike-slow wave complexes (absences). Treatment with ketogenic diet showed clinical improvement with the reduction of paroxysmal dyskinesias.

Keywords: Glucose transporter 1 deficiency syndrome; Movement disorder; Paroxysmal dyskinesia; Ketogenic diet; *SLC2A1* gene

1. Introduction

Glucose transporter 1 deficiency syndrome (GLUT1-DS) is a neurometabolic disorder, caused by a mutation in *SLC2A1* gene. GLUT1-DS results from impaired transport of the glucose molecules through the blood–brain barrier in the central nervous system [1]. Patients with classical phenotype present with epileptic encephalopathy, developmental delay, acquired microcephaly and movement disorders, while patients with non-classical phenotype present with cognitive deficit and paroxysmal non-epileptic episodes, provoked by infection, exercise, fasting, stress and emotions [2]. Classical phenotype can be early onset if clinical features appear before 2 years of age, and late onset, if clinical features appear later. However, today, this distinction between phenotypes is doubtful as the clinical features overlap.

The diagnosis of GLUT1-DS can be confirmed by hypoglycorrhachia in the presence of normoglycaemia with a CSF:plasma glucose ratio of <0.4 [1]. However,

* Corresponding author at: Center for Pediatrics, Children's Hospital, Affiliate of Vilnius University Hospital Santariskiu Clinics, Santariskiu st. 4, 08406 Vilnius, Lithuania. Fax: +370 272 0283.
E-mail address: sandra.melnik10@gmail.com (S. Juozapaite).

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in patients with the late-onset phenotype, the CSF:-plasma glucose ratio can be <0.59 [3,4]. Mutation analysis of *SLC2A1* gene is also available. Treatment with a ketogenic diet improves seizures, movement disorders and cognitive impairment. This case report describes a 16 years old patient with late onset GLUT1-DS, manifesting with epilepsy and treatment resistant movement disorders.

2. Case presentation

A 3 year 6 month old girl presented with paroxysmal exertion-induced and paroxysmal non exertion-induced dyskinesias (rapid jerking of one or both lower extremities, falling down or developing rolling gait), lasting 15 min to 4 h. During these episodes, the patient was able to draw and speak. Episodes occurred 3–4 times monthly.

Her family history was unremarkable. The patient showed no dysmorphic features and her head circumference followed the 50th percentile. Neurological examination revealed no pathology. Awake EEG during paroxysmal episodes showed diffuse slowing of background activity without epileptiform discharges. No significant changes were found on head CT scan and head MRI. Her karyotype analysis was normal (46, XX). Selective screening for inborn errors of metabolism was negative.

At the age of 5 years and 2 months, she experienced her first generalized tonic–clonic seizure after tonsillitis and fasting. On interictal video EEG we found generalized 3–3.5 Hz spike-wave complexes. so patient was diagnosed with idiopathic generalized epilepsy and treatment with valproic acid (VPA) was initiated. Due to severe side effects treatment with VPA was discontinued and patient was started on topiramate (TPM), later on oxcarbazepine (OXC). Epileptic episodes disappeared, however stereotypic paroxysmal exertion-induced and paroxysmal non exertion-induced dyskinesias occurred 1–2 times monthly with various duration (10 min – 2 h).

At the age of 7 years and 5 months, patient developed absence type of seizures, with characteristic EEG features (Fig 1). As her paroxysmal dyskinesias intensified, mainly after emotional stress caused by fighting with parents and friends, we performed treatment trials with ethosuximide (ETX) and lamotrigine (LTG).

At the age of 8 years and 2 months, her movement disorders intensified again after varicella infection and fasting, so LTG was changed to levetiracetam (LEV) and later to carbamazepine (CBZ). Paroxysmal episodes continued with CBZ but absences responded to ETX. During the next 5 years, she was treated with ETX

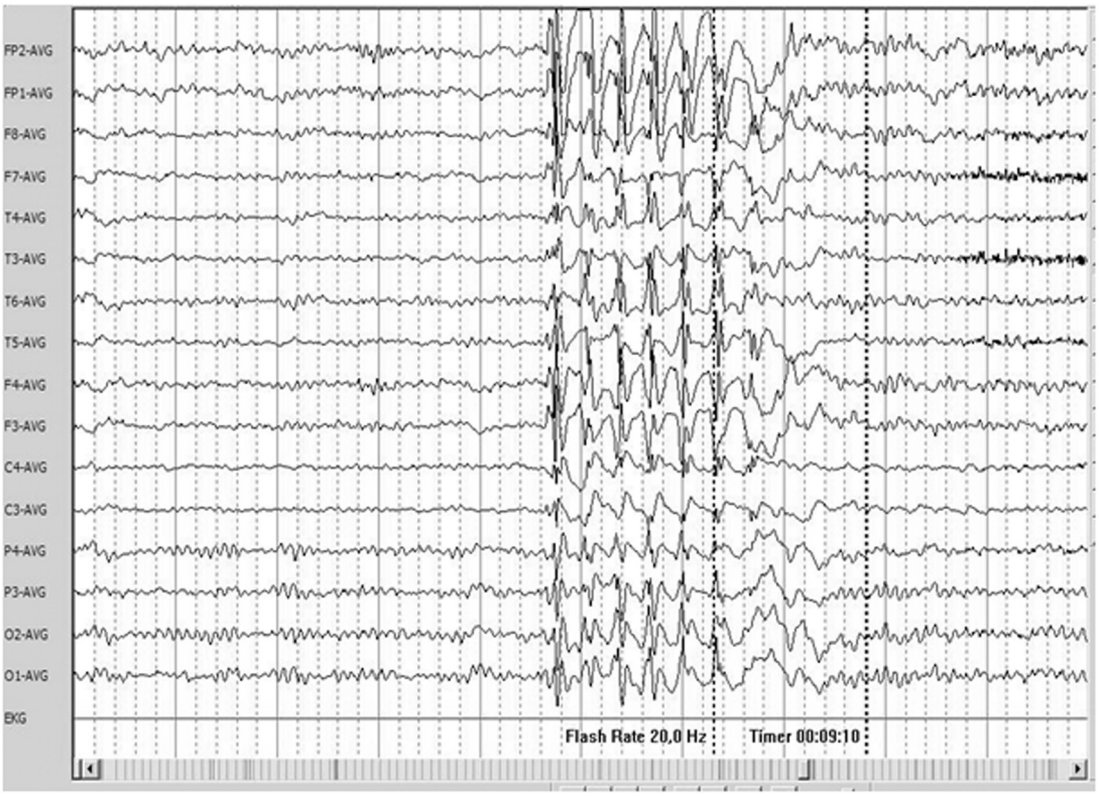

Fig. 1. Interictal EEG showed normal background activity with generalized spike-slow wave complexes, lasting 2–3 s, provoked by photostimulation while ictal EEG demonstrated longer 10 s episodes, provoked by hyperventilation.