

Glucose transporter type 1 deficiency syndrome (GLUT1-DS) – delayed diagnosis and treatment. A case report

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SUMMARY

Background. Glucose transporter type 1 deficiency syndrome (GLUT1-DS) is a treatable metabolic disorder caused by mutation in the *SLC2A1* gene. The functional deficiency of the GLUT1 protein leads to impaired glucose transport into the brain, resulting in a spectrum of neurological phenotypes. The most severe classic phenotype comprises infantile-onset epileptic encephalopathy associated with delayed development, acquired microcephaly, motor coordination disturbances, and spasticity. The less severe clinical features, such as paroxysmal exercise-induced dystonia with or without epileptic seizures, are also observed.

Aim. Hypothesis, that one possible treatment option entails intrathecal injection of glucose.

Material and Methods. We describe a woman, who was diagnosed as having epilepsy and treated for years with different antiepileptic drugs with no clinical effect. She had only two generalized tonic clonic seizures in her life. The patient suffered from increasing frequency of the paroxysmal involuntary movements of lower limbs, leading to gait disturbances and falls, which were misdiagnosed as epileptic seizures. The jerks of the head and limbs were observed from the first months of her life. The symptoms were provoked by stress and exertion. Additionally, mild intellectual disability was noted during her growth.

Results. Glucose concentrations in cerebrospinal fluid were low. The *SLC2A1* gene analysis resulted in the identification of a heterozygous missense mutation p.Arg333Trp. identification. The diagnosis of GLUT1-DS was confirmed.

Conclusion. Delayed diagnosis resulted in many problems with the acceptance of the ketogenic diet, which is considered the treatment of choice in GLUT1 deficiency syndromes. To our knowledge, this is the first case report of GLUT1-DS diagnosis occurring in adulthood and published in Poland.

Key words: GLUT-1 deficiency · ketogenic diet · epilepsy · dystonia

BACKGROUND

Glucose is the major carbon and energy source of nerve cells, supporting brain growth and neural excitation. The glucose transporter of capillary endothelial cells

located at the blood brain barrier (BBB), facilitates the passive flux of glucose from blood to brain (Wong et al., 2007) and is also responsible for astrocyte glucose

transport. Glucose membrane transporters (GLUT) proteins are encoded by the *SLC2* genes. They are members of the major facilitator super family (MFS) which includes 14 different types of GLUT transporters in humans. Several rare congenital disorders, due to mutations in various *SLC2* genes have already been reported (Pearson et al., 2013). The *SLC2A1* gene (MIM 138140) is the only one in which pathogenic variants are known to cause various glucose transporter type deficiency syndromes: GLUT1-DS type1 (MIM 606777), GLUT1-DS type 2 (MIM612126), GLUT1-DS with pseudo hyperkalemia and hemolysis (MIM 608885) and idiopathic generalized epilepsy-12 (MIM 614847).

Haplodeficiency of GLUT1 due to heterozygous pathogenic variants in the *SLC2A1* gene, mainly of an autosomal dominant inheritance, leads to chronic hypoglycorrachia (decreased cerebrospinal fluid glucose concentration) and neurological dysfunction, which constitute the defining features of the GLUT1-DS (Pascual et al., 2007; De Vivo et al., 1991; Pascual et al., 2004). The GLUT1-DS usually presents as a classic form, with epileptic seizures (90%), but about 10% of patients are seizure-free. The phenotypic spectrum of GLUT1-DS is known to be a continuum between the classic phenotype and the dystonia 18, atypical childhood absence epilepsy, myoclonic astatic epilepsy, and paroxysmal non-epileptic findings (ataxia, choreoathetosis, dystonia, and alternating hemiplegia).

The most severe GLUT1-DS type 1 is characterized by infantile-onset epileptic encephalopathy associated with delayed development, acquired microcephaly, motor incoordination and spasticity (Brockmann, 2017; De Giorgis, Veggiotti, 2013). The onset of seizures, is usually characterized by apneic episodes, staring spells, and episodic eye movements. They occur within the first 4 months of life. Different types of seizures have been described – generalized tonic-clonic, absence, complex partial, myoclonic (focal or generalized), drop seizures, tonic (focal or generalized), simple partial, infantile spasms. However, the generalized tonic-clonic and absence seizures are the most common and often appear simultaneously (Brockmann, 2017). Other paroxysmal findings include intermittent ataxia, confusion, lethargy, sleep disturbance, and headache. Varying degrees of cognitive impairment can occur, ranging from learning disabilities to severe intellectual disability. GLUT1-DS type 2 is a clinically variable disorder characterized primarily by paroxysmal exercise-induced dyskinesia (DYT18) with onset in childhood.

The dyskinesia involves transient abnormal involuntary movements, such as dystonia and choreoathetosis, induced by exercise or exertion, and affects the exercised limbs. Some patients may also have epileptic seizures, most commonly childhood absence epilepsy. Mild intellectual disability may also occur. In some patients a macrocytic hemolytic anemia has been described.

Under chronic brain glucose deprivation caused by GLUT1-DS, exogenous or endogenous substrates (i.e., ketone bodies and fatty acids) may serve as alternative fuels to maintain neural function. The ketogenic diet is proved to be effective in controlling seizures and other paroxysmal events associated with GLUT1-DS (Friedman et al., 2006; Leary et al., 2003; Pérez-Dueñas et al., 2009).

AIM

To discuss the possibility of different forms of GLUT1-DS therapy, especially in adult patients. We hypothesized, that one possible treatment option may be by use of intrathecal glucose injection.

MATERIAL AND METHODS

A twenty year old woman was admitted to the neurological department with a diagnoses of drug resistant epilepsy. Her historical data were: the patient was born in at 39 week of pregnancy, birth weight 2900 g (10–25 c), length 53 cm (10–25 c), OFC 33cm (3–10 c) with an Apgar Score 8. In the first week of her life she was treated with antibiotics because of otitis. Since that time, she was under neurological observation because of “uncontrolled” eye (nystagmus), head, limb movement, twisting trunk, “stiffness” and fatigability of lower limbs. Subsequently, sudden “absence states”, “balance disturbances” were observed, sometimes followed by collapses and accompanied by increased muscles strains. The attacks resulted from even little effort. Tension of muscles was decreased in limbs. Her psychomotor development was delayed. She started walking at the age of 2 y and 6 months. She began to speak at the age of 3 years. At the age of four, the first generalized epileptic seizure with prominent tonic phase, accompanied by salivation, oral automatisms and loss of consciousness was observed. Epilepsy was diagnosed and valproic acid (VPA) was administered 300 mg per day. The second and the last epileptic seizure was observed when she was six. She had been taking different antiepileptic drugs for the next sixteen years, because of sudden involuntary movements and sudden collapses which

Table 1. Clinical symptoms during the course of disease

Age	Symptoms and signs
Infancy	“Uncontrolled” eyes (nystagmus) Head and limbs movement Trunk twisting “Stiffness” Fatigability of lower limbs
Childhood (early)	Sudden “absence states” Balance disturbances Collapses Increased muscles strains The attacks resulted from even little effort Tension of muscles decreased in limbs The psychomotor development delayed Delayed walking, at the age of 2,5 yrs Delayed speech, at the age of 3 yrs The first generalized epileptic seizure at the age of 4 yrs The second and the last epileptic seizure at the age of 6 yrs
Childhood	Sudden involuntary movements with collapses Optic-motor coordination disturbances
Adolescence	Paroxysmal speech difficulties (“aphasia”) with pyramidal symptoms in right limbs and involuntary movements of lower limbs Gait disturbances lasting for several hours leading to falls, escalated by exertion Paroxysmal incidents during awaking and falling asleep (myoclonic jerks) Headaches Writing disturbances Abrupt body stiffness Tightened eyes followed by head and trunk dropping on a desk Incidents of hypoglycemia connected with symptoms
Adulthood	Tremor of upper limbs

were diagnosed as epileptic seizures. In spite of many treatment modifications no clinical effect was noted. In the following years, the incidence of muscle fatigability, balance disturbances and anxiety lasting up to one hour, were often observed.

The patient was consulted by orthopedist (flat feet and knees valgus was found) and an otolaryngologist with no abnormalities in the examination. Psychological tests revealed intellectual norm, however with presence of many slight abnormalities such as speech, causal-effective thinking, graphomotor dexterity, sight perception, apprehension accuracy, knowledge of norms, manual dexterity and optic-motor coordination disturbances were noted.

Two sudden incidents of symptoms were diagnosed as transient ischemic attacks. During those attacks patient presented with speech difficulties defined as motoric aphasia and pyramidal symptoms in right limbs, with involuntary movements of lower limbs and gait disturbances leading to falls. They lasted for several

hours. Symptoms were intensified by exertion, particularly during walking (limpness distance was three hundred meters). Moreover, the mother observed paroxysmal incidents during awaking and falling asleep which seemed to be limbs and facial muscles myoclonic jerks. A further attack, described as headache, writing disturbances, abrupt body stiffness, consciousness disturbances, tightened eyes followed by head and trunk dropping on a desk was observed. At the age of 20 tremor of upper limbs leading to spill of drinks appeared. Furthermore, incidents of hypoglycemia and associated symptoms were diagnosed. We summarized the clinical symptoms during the course of the disease in Table 1. During the course of the disease the incidents occurred with frequency of one per two years.

Antiepileptic treatment was modified using lamotrigine (LTG), VPA, carbamazepine (CBZ), levetiracetam (LEV) in different combinations and doses. In the course of the disease, arterial hypertension was diagnosed additionally.



Figure 1. Dystonic postures of upper and lower limbs during involuntary movements.

Many diagnostic tests were performed so as to identify the cause of symptoms: MRI scans, EMG with myasthenic and tetany tests, RTG of the hips, vertebral column and feet did not reveal any abnormalities. The EEG at the beginning was normal. However, subsequent recordings revealed sharp waves in temporal lobes, sometimes generalized. In one EEG recording general 3 Hz delta waves and spike – slow wave complexes with high amplitude, activated by hyperventilation.

Because of a suspicion that the patient suffered from a metabolic disease, various diagnostic tests were undertaken. However normal blood levels of creatine kinase, cortisol, TSH activity and cyanocobalamin, and folic acid were noted. Plasma amino acid levels, organic acid profile, acylcarnithines and transferine isoforms pattern were also normal.

However concentrations of free carnitine in urine (20 $\mu\text{mol/g}$ [N: 25–330]) and in serum were decreased to 27 $\mu\text{mol/l}$ [N: 35–70], whereas lactic acid concentrations in a blood were a little bit elevated (20.66 mg/dl [N: 4.5–19.8]), gasometry parameters and alpha glucosidases were normal. Mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibers (MERFF), neuropathy, ataxia, and retinitis pigmentosa (NARP) and Leigh's syndrome were excluded in genetic tests as

well as in histopathologic cutaneous-muscular biopsy examination. Test of breath chain enzymes activity revealed slightly reduced or normal activity for most enzymes except for citrate synthase, which was substantially elevated (354.2 nmol/min/m [N: 96.5–150.1]). Tetany and intellectual disability were diagnosed.

RESULTS

The patient was admitted to our neurological department when she was twenty years old to investigate the reason of “drug resistant epilepsy”. She was treated with LEV 2000 mg/24h and VPA 1200 mg/24h at time of admission.

During the hospitalization, there were no epileptic seizures recorded, but the involuntary movements of lower limbs resembling dystonic postures were frequently observed (Fig. 1). EEG revealed only diffuse, single slow waves, without sharp waves or spikes. EMG composed of conductivity, muscle and myasthenic tests was normal. Lumbar puncture was performed and revealed normal t cytosin (4/3) and protein concentration (30.5 mg/dl) with decreased level of glucose in cerebrospinal fluid (30 mg/dl). The patient was referred for genetic tests and genetic consultation with a suspicion of GLUT-1 deficiency syndrome. Genetic evaluation apart from small head circumference (<3 c) in

comparison to height (25 c) did not revealed specific dysmorphic features.

Treatment was modified by adding levodopa with benserazid with no clinical improvement. LEV discontinuation and reduction of VPA to 900 mg a day resulted in elongation of limping distance from 300 to 600 meters.

The sequence analysis of the *SLC2A1* gene revealed the presence of substitution c.997C>T in exon 8 of one allele leading to missense mutation of protein p.Arg333Trp (patients genotype c.[997C>T];[=]; p.[(Arg333Trp)];[=]). The identified mutation is responsible for GLUT1-DS1 syndrome.

The patient was informed about the ketogenic diet as the treatment of choice in this case, but she did not accept the recommendation. Subsequently, acetazolamide was prescribed and during the first three months of therapy a notable clinical improvement was observed, with less frequent involuntary movements, further limping distance elongation and self-reliance improvement. Afterwards, another dystonic status, resistant to standard therapy and lasting approximately eight hours occurred. The patient was hospitalized.

Finally, the patient and her mother accepted to the ketogenic diet therapy. Since that time involuntary movements stopped for several months. After that time the involuntary movements appeared again. The therapy was finally ineffective.

DISCUSSION

The diagnostic criteria for GLUT1-DS include: epileptic seizures, developmental delay, complex movement disorder, and fasting EEG changes (Klepper, Leiendecker, 2007). However, some case reports, without classical course of the disease, have been reported. It was for this reason that broadening of GLUT1-DS phenotype spectrum to patients with ataxia and mental retardation but without seizures, individuals with dystonia and choreoathetosis, as well as rare cases with absence seizures and no movement disabilities, occurred. Other reported paroxysmal findings include intermittent ataxia, confusion, lethargy, sleep disturbance, and headache. Varying degrees of cognitive impairment can occur, ranging from learning disabilities to severe mental retardation (Pons et al., 2010). In all these cases symptoms exaggerate after exertion. Hypoglycorrhachia (CSF glucose less than 40 mg/dl) and low CSF lactate are essentially diagnostic for the disorder. Laboratory criteria include also, reduced erythrocyte glucose

uptake and/or decreased GLUT1 immunoreactivity in erythrocyte membranes. Thus the lumbar puncture and CSF examination should be the obligatory test in all drug resistant patients with epileptic seizures or any other paroxysmal incidents. Hypoglycorrhachia should be followed by genetic tests to exclude the GLUT1 mutations. Detection of the heterozygous mutations in the *SLC2A1* gene confirms this diagnosis. In our patient the missense mutation p.Arg333Trp, which is responsible for GLUT1-DS1 syndrome was identified.

Because of wide variety of symptoms, the exact diagnosis is often difficult and delayed. Epileptic seizures, being the most common clinical problems, cause the decision about introduction and later following modifications of doses, usually unsuccessfully. It means that the proposed treatment maybe wrongly provided for years, making the disease pseudo “drug resistant” (Pong et al., 2012). Our patient suffered from paroxysmal, involuntary movements provoked by stress or exertion without consciousness disturbances, and she was treated as a patient with myoclonic epilepsy using many antiepileptic drugs without improvement.

The ketogenic diet is the treatment of choice in the GLUT 1 deficiency syndrome, as it provides an alternative source of energy to the brain (Klepper, Leiendecker, 2007). It has been reported that the ketogenic diet effectively controlled seizures and other motor symptoms of GLUT1 deficiency, but was less effective on cognitive symptoms (Wang et al., 2005). There are some case reports describing good clinical response to ethosuximide for seizure treatment and to acetazolamid for paroxysmal dyskinesia therapy (Anheim et al., 2011; Gramer et al., 2012). Unfortunately, the ketogenic diet is unacceptable for many people, especially, when they start to use it in adulthood. Despite the efficacy, ketogenic diets deliver only ketone acids to the brain. Therefore, it does not resolve the problem with glucose supply. Ketogenic diet therapy does not prevent or reverse all of the symptoms associated with GLUT1-DS and there is a need to develop alternative, more effective, therapies in the field. It seems reasonable to search for another way to supply the brain with glucose.

CONCLUSIONS

One of the possible ways of treatment seems to be glucose intrathecal injection although there have been no publications to-date about this therapeutic approach. As this kind of therapy is associated with possible side effect and complications, it could probably be consid-

ered in cases of adult patients who did not respond well to other potential drugs and also in patients who did not choose to follow the ketogenic diet. It can be considered in acute clinical states, for instance, dystonic states. Further preclinical and clinical trials are needed.

CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflicts of interests.

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