Phenotypic diversity of GLUT1 deficiency: A case report.

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Glucose transporter type-1 deficiency syndrome (GLUT1DS) (OMIM # 606777) is due to impaired glucose transport into the brain caused by mutations in *SLC2A1* encoding a trans-membrane protein. It is often caused by *de novo* mutations but also can be inherited in an autosomal dominant and, rarely, in an autosomal recessive pattern. Missense, nonsense, frame shift, splice site, translation initiation mutations or multiple exon deletions lead to absence or loss of function of the transporter. Although many correlations between phenotypes and genotypes have been discussed in the literature, there is evident heterogeneity in terms of clinical, laboratory and genetic findings.

OBJECTIVES

Glucose transporter type-1 deficiency syndrome has classical and non-classical phenotypes which have been discussed as different subgroups with varying combinations of symptoms and findings in literature. The classical form is basically characterized by early infantile seizures, developmental delay, developmental microcephaly, and movement disorders[1]. Hypoglycorrhachia and low CSF lactate are diagnostic features. Here we present a case with infrequent, self-remitted, infantile-onset seizures, experiencing new-onset ataxia and subtle attention-deficit symptoms with normal intelligence. Then discuss the points affecting phenotypic heterogeneity and the importance of ketogenic diet treatment.

CASE REPORT

A 6½-year-old girl from a non-consanguineous family of Turkish origin was admitted to the hospital due to fatigue and gait disturbance noticed, when tired or hungry, during the last year. Her blood glucose level, incidentally controlled two hours after a meal was 47mg/dL. She had developed generalized tonic-clonic seizures at the age of six months, had valproic acid treatment for three years and had not been on medication for 1 ½ years. She gained walking at the age of 16 months, first single words at the age of 12 months, although her family had difficulty understanding some of her speech. Clinical examination showed ataxic tandem gait, dysmetria, mild speech impediment and signs of a mild attention-deficit disorder. The cranial and spinal MRIs and echocardiography were unremarkable. Electroencephalography showed bilateral anterior sharp-slow wave activity predominantly on the right. A gene panel for epileptic encephalopathies unravelled a heterozygous, pathogenic variant in the *SLC2A1* (NM_006516.4:c.680-11G>A). Further analysis of cerebrospinal fluid (CSF) in fasting state revealed hypoglycorrhachia (35 mg/dL), and the CSF/blood glucose ratio was 0.41 with normal lactate levels. A ketogenic diet was started with the diagnosis of GLUT1DS. After dietary change, improvements in gait and speech problems have been observed.

DISCUSSION

Despite the classical definition, three groups of the clinical picture have been suggested such as; (1) intellectual disability (ID) with epilepsy or a movement disorder, (2) “epilepsy-dominant” phenotype with or without movement disorders but without ID, and (3) “movement-disorder-dominant” phenotype without ID, nor seizures[2]. Regarding genetics, in missense mutations intellectual disability is expected to be milder, while in other types of mutations the frequency of movement disorder is higher and CSF/blood glucose ratio is likely lower. Nevertheless, the disorder has many exceptions. Patients with identical mutations are heterogeneous in terms of phenotype and severity, and in patients with movement disorders or milder phenotype the CSF/blood glucose ratio can be borderline or even normal[3]. Our patient had an intronic mutation creating a new splice acceptor site, which caused infantile-onset epilepsy, evolving into ataxia, mild dysarthria and subtle psychiatric signs. In literature, although some of the information is not avaliable in some of the cases with the same mutation as our patient, drug-resistant epilepsy with normal intelligence was defined in a 7-year-old girl whose complaints started when 1 years old[3]. Our case is similar to her regarding epilepsy and normal intelligence, but also differs in terms of accompanying movement and speech disorders. It has been suggested that the clinical subgroups of patients change by age, possibly due to physiological changes in local cerebral glucose utilization during brain development[4].

In our case, we think that the mentioned evoluion has been observed which will hopefully benefit from therapautic interventions; especially ketogenic diet.

CONCLUSION

Further genetic testing in early infantile epilepsy and ID is critical regarding GLUT1DS. Considering the diagnostic delay extending up to 6 years in many cohorts and broad spectrum of symptoms, it is also important to prioritize a lumbar puncture to measure CSF glucose because ketogenic diet improves the frequency of seizures, movement disorders and even cognitive functions partially.

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