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Case Report

A novel mutation in SLC2A1 gene causing GLUT-1 deficiency syndrome in a young adult patient

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GLUT-1 deficiency syndrome is a rare, frequently unrecognized metabolic encephalopathy that is probably underdiagnosed. Although developmental delay, acquired microcephaly, spasticity, and impaired coordination were initially described as the classic findings, mild cases with no pronounced neuromotor compromise have since been included in the broad clinical spectrum with new mutations being identified more recently. We report a case of myoclonic seizures not responding to anti-epileptics since the age of one year in a 17-year-old patient with a normal phenotype and neuromotor development. Previously unreported p.Phe389Leu mutation was determined in the *SLC2A1* gene in our patient. This case will be useful in clarifying the phenotype of GLUT-1 deficiency and reveals a new pathogenic mutation.

Key words: ***SLC2A1 gene, GLUT-1 deficiency syndrome, drug-resistant epilepsy.***

Glucose provides energy for brain cells. Glucose transporter 1 (GLUT-1) is a membrane protein encoded by the *SLC2A1* gene that plays a crucial role in glucose transport over the blood-brain barrier. The mutation in *GLUT-1* known as GLUT-1 deficiency syndrome (GLUT-1 DS; OMIM #606777) is characterized by low levels of glucose in cerebrospinal fluid (CSF) despite normoglycemia.[1] GLUT-1 deficiency results in a range of symptoms that may exhibit significant variation from one patient to another. Approximately 150 GLUT cases have been reported, mainly from the USA, Europe and the East Asia.[2] To the best of our knowledge, our patient represents the second case of GLUT-1 DS from Turkey.

Case Report

General information and clinical manifestations

A 17-year-old male patient was born to healthy non-consanguineous parents after an uneventful pregnancy. Birth weight and head circumference were normal. The first infantile myoclonic seizure occurred at one year of age. Seizures continued at the same frequency and duration until the age of 17. The seizures did not respond to anticonvulsants, such as levetiracetam, carbamazepine or valproic acid. Cerebral magnetic resonance imaging (MRI) and electroencephalograms elicited no specific findings.

Laboratory tests

Laboratory tests revealed normal complete blood count and biochemistry. Lumbar puncture performed after 7-h fasting revealed a normal CSF glucose level in a normoglycemic setting (blood glucose, 93 mg/dl; CSF glucose 47mg/dl, and CSF to blood glucose ratio 0.50).

This study was presented at the 54th Annual Meeting of the European Society of Paediatric Endocrinology (ESPE), 1-3 October 2015, Barcelona, Spain

Genomic analysis

Genomic DNA was extracted from the patient's and parents' peripheral blood leukocyte was used as the template for polymerase chain reaction (PCR). Compatible primers were used to yield DNA fragments spanning the entire coding region and intron–exon boundaries of *SLC2A1*.[3] The PCR fragments were analyzed using automated sequencing.

A heterozygous missense mutation was determined in the *SLC2A1* gene (c.1167C>A, Genebank accession no. NM_006516.2, p.Phe389Leu). Analysis of the parents confirmed that the *SLC2A1* mutation had occurred de novo. Genomic DNAs of the proband's father and mother exhibited wild type sequences (Fig. 1). The mutation was identified as potentially injurious by both PolyPhen-2 and SIFT.

Written informed consent for this report was obtained from the family.

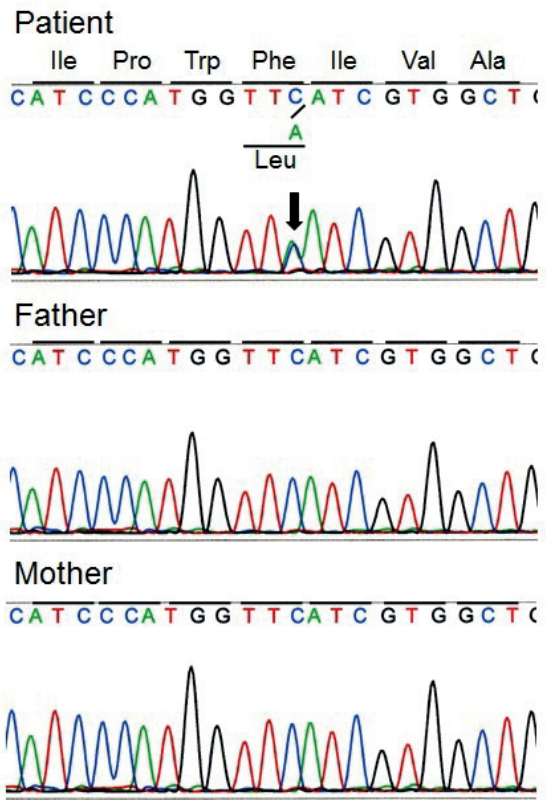

Fig. 1. A heterozygous missense mutation at codon 389 (p.Phe389Leu; c.1167C>A) was found in the genomic DNA of the patient. Both genomic DNAs of father and mother of the proband showed wild type sequences.

Discussion

Our patient was followed-up due to antiepileptic-resistant epilepsy for several years. GLUT-1 DS was finally diagnosed at the age of 17. This syndrome is a rare, underdiagnosed encephalopathy. One possible reason for non-diagnosis or late diagnosis is that the high disease suspicion threshold means that diagnosis may only be considered with clinical findings such as developmental delay, acquired microcephaly, spasticity, and poor coordination in the years when it is first identified. Greater sharing of international data since the disease was first diagnosed means that increasing information is becoming available concerning the clinical spectrum of the mutation and the characteristic features of pathogenic mutations. Wide clinical variation has thus been revealed in patients carrying *GLUT-1* mutation. This has particularly resulted in broader recognition of milder phenotypes. Our patient was normal in terms of phenotype and neuromotor development. Significant numbers (15%) of patients with a non-classical phenotype incorporating developmental delay and movement disorders have been observed among cases of Glut-1 DS.[4] The spectrum of intellectual compromise may range from very severe to very mild.[5,6] Awareness of the broad range of potential clinical phenotypes associated with Glut-1 DS will facilitate earlier diagnosis of this treatable neurological condition.

The CSF to serum glucose ratio in GLUT-1 deficiency is characteristically low, under 40%. This ratio was recently reported at between 24% and 49%, with a mean value of approximately 37%, in one case series.[7] Our patient's CSF to serum glucose ratio was 50%, above this upper threshold. Our patient's relatively high CSF to serum glucose ratio may explain the absence of classic findings and the isolated myoclonic seizures. However, this can only be confirmed through investigation of correlation between clinical findings and CSF to serum glucose ratios in larger patient series.

Previously unreported, de novo heterozygous missense mutation was determined in our patient. Although GLUT-1 deficiency was originally described as exhibiting an autosomal dominant pattern of inheritance, family

members have only been affected in 10% of case reports to date (autosomal dominant inheritance pattern), and approximately 90% have a de novo heterozygous mutation in *SLC2A1*.[5]

GLUT-1 mutations may take the form of missense, nonsense, frameshift, splice site, multiple exon deletion or complete gene deletion. Missense mutations constituted more than 40% of all mutations in two large series in the literature, and were the most prevalent mutation types.[4-8] No characteristic mutation or phenotype-genotype correlation has been determined to date.

This syndrome has largely been seen in North America, Europe and East Asia.[2] Our patient is the second genetically diagnosed case of GLUT-1 DS from Turkey. The other Turkish patient was a 7-year-old girl with a mutation (p.r126c) in the *SLC2A1* gene.[9]

Our patient was referred to another center to be started on a ketogenic diet and was placed under observation in terms of response to treatment.

Our case adds new phenotype findings of GLUT-1 deficiency to the literature and reveals a probable new pathogenic mutation. Although GLUT-1 deficiency is a rare condition, it should be considered in patients with drug-resistant epilepsy even with a normal phenotype and neuromotor development.

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