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Letter to Editor

A Patient with Glucose Transporter Type 1 Deficiency Syndrome: Paroxysmal Choreoathetosis and Cerebral Positron-Emission Tomography Findings

Dear Editor,

Glucose transporter type 1 deficiency syndrome (GLUT-1 DS) is one of the metabolic disorders that can cause mental-motor delay, seizures, and movement disorders.[1] This autosomal dominant inborn error of metabolism results in defective glucose transport and consequently a reduced supply of glucose to the brain. A low level of glucose in the cerebrospinal fluid (CSF) is the main parameter that makes it possible to diagnose this syndrome. The cause is reported to be some novel mutations discovered in the *SLC2A1* gene, which is located on the short arm of a chromosome.[1,2] The ketogenic or Atkins diet provides the brain with an alternative source of energy as a choice of treatment.[3,4]

Some of the well-known clinical presentations of GLUT-1 DS are early-onset epilepsies, motor-mental developmental delay, acquired microcephaly, hypotonia, spasticity, and ataxia; however, its phenotype is highly variable. Several GLUT-1 DS cases have been studied from the point of view of hyperkinetic movement disorders.[5,6] It is usual for these patients to first present with chronic facial or limb dystonia, parkinsonism, and paroxysmal exercise-induced dyskinesia (PED), including dystonic, choreoathetotic, and ballistic movements.

There are limited studies on cerebral F18-fluorodeoxyglucose positron-emission tomography (FDG PET) in these patients.[7] Here, we describe a patient with a GLUT-1 mutation who presented with severe paroxysmal choreoathetosis. This is a molecularly proven case whose cerebral F18-FDG PET findings are reported little in the literature.

The patient was a 7-year-old boy who was born to unaffected, nonconsanguineous parents at term following an uncomplicated pregnancy and delivery. The child was delayed in achieving major milestones; he did not walk and acquire his first words until the age of 2 years. He developed an unsteady walk at age 2.5 years with frequent falls that were not associated with a loss of consciousness. His routine blood and urine analysis, electroencephalogram and magnetic resonance imaging revealed normal results. His movement disorder could be spontaneous or precipitated by fasting. During the episodes, he consistently showed unpredictable and markedly jerky-like movements resembling choreoathetosis, which were randomly distributed over parts of the body and would interfere with sitting, eating, standing, walking, or playing. These movements were prominent in the limbs, resulting in gait disturbances and falls. With progressing age, attacks gradually became apparent, occurring every 1–3 weeks and lasting 15–90 min. He was started on valproic acid, which was followed by phenobarbital at the age of 4 years. The frequency and intensity of the attacks decreased with the therapy but without prompt response. He had mild intellectual disability, and occupational therapy assessment showed difficulties in fine motor skills, especially in writing. His physical and neurologic examinations were within normal limits, except for brisk reflexes in the lower extremities.

The local ethics committee of Istanbul Faculty of Medicine approved this case study. Informed consent for the case investigation was obtained from the family in accordance with national guidelines. In a lumbar puncture, his CSF was found to have a glucose concentration of 36 mg/dL. This was 41% (normal >60%) less than the concentration of serum glucose, which was found as 87 mg/dL. Performed at Duncan Guthrie Institute of Medical Genetics in Glasgow, DNA sequencing for the *SLC2A1* gene demonstrated a heterozygous substitution of a single-base pair. As a result, an arginine residue was replaced with that of histidine at position 400 in the SLC2A1 protein (c. 1199G>A; p. Arg400His). Neither the patient's parents nor his sister had the mutation. FDG PET revealed hypometabolism in bilateral mesial temporal lobes, along with the cerebellar cortex [Figure 1]. After the identification of the *SLC2A1* gene mutation, our patient was started on a modified Atkins diet. His cognitive skills remained stable, and his attacks decreased by approximately 80% with an improvement in energy level, alertness, and concentration 2 weeks after the onset of the Atkins diet. During interruptions of the Atkins diet, his attacks reappeared [Video 1].

Discussion

The classic phenotype of GLUT-1 DS is characterized by early-onset childhood epileptic encephalopathy, motor and mental delay, as well as head growth deceleration,

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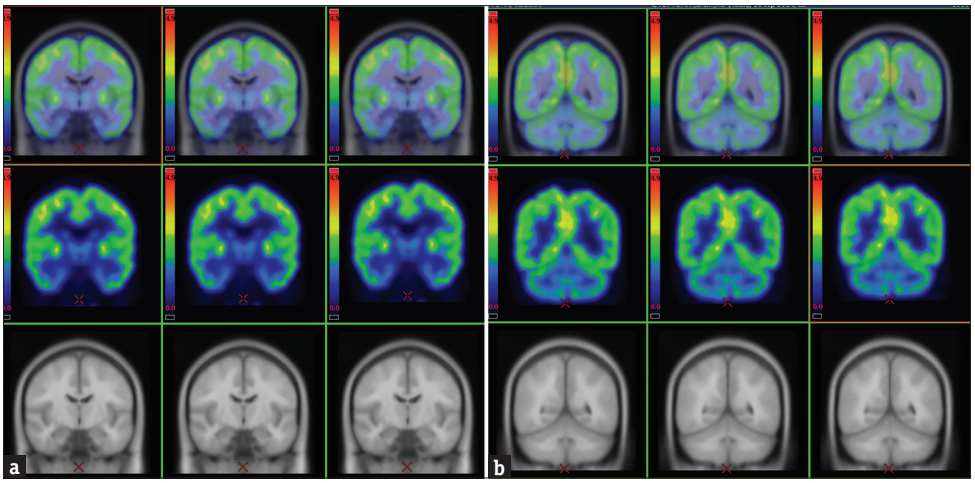


Figure 1: Coronal slices of F18-fluorodeoxyglucose positron-emission tomography and fusion positron-emission tomography-computed tomography images of the patient show bilateral hypometabolism in the mesial temporal (a) and cerebellar lobes (b)

resulting in acquired microcephaly and a movement disorder with ataxia and spasticity.[1,5] However, this definition has been enlarged with several cases and case series during the past 25 years worldwide.[5,6] Intermittent ataxia, chronic or paroxysmal choreoathetosis, and dystonia have been described. Of the paroxysmal movement disorders, the one most widely seen is PED, which can occur alone or in association with epilepsy.[8] Paroxysmal events described by Pons *et al*. in 28% of their series had no epileptic characteristics.[9] Seizures can take many forms as stated below: absence seizures, generalized tonic − clonic seizures, complex/simple partial seizures, and myoclonic seizures.[8]

There are a large number of studies on complex movement disorders in variable combinations and different paroxysmal events, including dystonia, chorea, stereotypes, tremor, myoclonus, dystonic myoclonus, dyspraxia, alternating hemiplegia, writer's cramp, and migraine.[9-12] These paroxysmal events generally do not cause loss of consciousness and may include gait disturbances, as well as isolated dysphoria. To a degree, our patient exhibited similar symptoms. He also had hunger-induced choreoathetosis, making it impossible for him to walk. On the other hand, Gaspar *et al*. described a patient with a very similar polymorphism.[13] Their patient had a c. 1199G>T; p. R400 L, whereas the patient reported here had a c. 1199G>A; p. Arg400His. The patient reported by Gaspar *et al*. presented with myoclonic seizures in infancy and went on to develop acquired microcephaly, ataxia, absence seizures, and generalized tonic − clonic seizures.

To the authors' knowledge, the number of studies on functional imaging of GLUT-1 DS patients is very limited.[7,8] Pascual *et al*. reported that with a global decrease in cortical uptake, more severe hypometabolism was found in the mesial temporal regions and thalami.[7] This metabolic footprint was relatively constant in all patients regardless of age, seizure history, or therapies, and therefore constitutes a radiologic signature of the disease. Having performed studies on a series of patients with co-occurring PED and epilepsy, Suls *et al*. reported that, according to their FDG PET findings, glucose metabolism relatively increased in the putamen and mid temporal cortex bilaterally but decreased in the thalamus bilaterally.[8] They added that when a patient had more frequent PEDs, the putamen hypermetabolism became more pronounced. Of note, impaired glucose metabolism is already known to affect the area responsible for extrapyramidal movement disorders. Hypometabolism was detected in the mesial temporal area of our patient. It may, therefore, be suggested that this metabolism can affect a larger network in the brain of a patient with movement disorders but without epilepsy. The structures where hypometabolism was present were not necessarily those thought to routinely exhibit hypermetabolic rates. In metabolic diseases, regional pathophysiology may be explained by a particular metabolic pathway regulated by the gene product. In this context, it is remarkable that our patient has cerebellar hypometabolism, a condition which, to the best of the authors' knowledge, is not discussed much in the literature.

The ketogenic or Atkins diet control seizures impressively and movement disorders in some patients with GLUT-1 DS, but cognitive symptoms do not recover.[3,4] The diet mimics the metabolic state of fasting but maintains ketosis by nutritional intake of fat rather than body fat. It is suggested in the literature that, as far as GLUT-1 DS is concerned, the ketogenic diet is less protective toward movement disorders than toward epilepsy. Therefore, it is remarkable that our patient

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responded very well to this treatment and his attacks decreased by approximately 80%.

GLUT-1 DS is a rare disorder, and its clinical spectrum is probably broader than recognized previously. The great variability among patients becomes even greater with age, and considerable delays in diagnosis may occur. This may explain why Hully *et al*., following their studies on a large series with GLUT-1 DS, concluded that genotype-phenotype correlations could be limited because of the huge variability of the presentation.[12] However, early diagnosis of this syndrome is essential because its symptoms are preventable and/or treatable. FDG PET studies on patients with GLUT-1 with different presentations may offer valuable data that could help to understand the interactions in the brain network and regional organizations. In return, it may make it possible for us to better understand the pathophysiology of GLUT-1 DS. Extensive studies on larger series are needed to have a clearer view of the disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given consent for images and other clinical information to be reported in the journal. The guardian understands that the patient's name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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