ABSTRACT: Background: A rare symptom of Glut1 deficiency syndrome (Glut1 DS) is hemiplegic migraine (HM).

Case: We report a patient with Glut1 DS with a mild phenotype. His leading symptom was HM. As an unusual complication of the initiation of a ketogenic diet (KD), our patient developed paroxysmal nonkinesigenic dyskinesia. Paroxysmal dyskinesia occurred first and exclusively at the initiation of KD.

Literature Review: There are a few case reports for HM in Glut1 DS. All patients had additional neurological symptoms. Regarding central nervous system symptoms such as paroxysmal dyskinesia triggered by KD, we found only 1 other case report.

Discussion: HM is part of the symptom complex of Glut1 DS and can be effectively treated by KD. Paroxysmal dyskinesia triggered by the initiation of KD should not lead to the discontinuation of the diet in Glut1 DS.

The phenotype of glucose transporter type 1 deficiency syndrome (Glut1 DS) is milder than the originally described classic course in about 10% of affected patients. The severe phenotype of Glut1 DS is associated with epileptic encephalopathy from infancy, developmental disorder, and microcephaly. Milder phenotypes have been described, which are associated with absence epilepsy or movement disorders such as ataxia, choreoathetosis, and paroxysmal movement disorders even without epilepsy. The diagnosis can be made by low glucose level in the cerebrospinal fluid < 3.3 mmol/L and the presence of a low liquor/blood–glucose ratio < 0.4 (range, 0.19–0.59). Normoglycemia has to be defined just before the lumbar puncture. Furthermore, the diagnosis can be genetically confirmed if a pathogenic variant is detected in the SLC2A1 gene. In case of suggestive clinical findings, the cerebrospinal fluid criteria or the detection of a pathogenic variant in SLC2A1 can lead to diagnosis either alone or in combination.

In Glut1 DS the malfunction of the glucose transporter at the blood–brain barrier causes a reduced energy supply to the brain. This can be circumvented by providing more ketone bodies as an alternative energy source. This requires a change in diet in the form of a ketogenic diet (KD).

The most common difficulties in initiating KD are hypoglycaemia, excessive ketosis, refusal to eat, and dehydration attributed to vomiting. Patients develop a compensated metabolic acidosis. If hypoglycaemia occurs in the absence of ketosis under KD, the reason needs to be clarified (eg, disorders of gluconeogenesis, fatty acid oxidation disorders), and the diet must be stopped. Reported long-term side effects are gastrointestinal disorders, dyslipidemia, growth disturbance, osteopenia, and nephrolithiasis. Often, the diet is poorly accepted and discontinued, mainly because of a challenging diet plan with high-fat and low-carbohydrate content.

A well-known symptom of Glut1 DS is paroxysmal dyskinesia (PxD) with paroxysmal exercise-induced dyskinesia being the most common PxD. PxD is characterized by attacks of spontaneous or induced uncontrollable dystonia, chorea, athetosis, and ballism in the limbs, face, and trunk. These attacks can last...
| Findings                                      | Current Publication | Almuqbil et al 2018 | Pellegrin et al 2017 | Weller et al 2015 | Mohammad et al 2014 | Pons et al 2010 | Rotstein et al 2009 |
|----------------------------------------------|---------------------|---------------------|----------------------|-------------------|--------------------|------------------|--------------------|
| Number of patients                           | 1                   | 1                   | 1                    | 1                 | 3 patients with paroxysmal hemiparesis in a collective of 57 patients with Glut1 DS | 1                 |
| Variant in the gene                           | c. 635G > A, p. (Arg212His): de novo | c. 79G > A (p.Gly27Ser): de novo | c. 418G > A; (p.Val104Met): de novo | c. 52G > C, (p.Gly18Arg): de novo | c. 929C > T, (p.Thr310Ile): de novo | n/a              | c.277C > T, p. (Arg93Trp): de novo |
| CSF glucose and/or liquor/blood glucose ratio | Normal apart from an arachnoidal cyst | During episode of hemiparesis: hypoperfusion contralateral to paresis in ASL-PWI and MRA. Repeat MRI 1 month later was normal | Normal         | Normal apart from a small, nonspecific white matter abnormality | Normal         | n/a              | Normal              |
| MRI                                          | Interictal epileptiform activity left or right-frontal, in part bifrontal | Interictal generalized epileptiform activity | EEG slowing contralateral to hemiparesis in the phase of hemiparesis | Interictal focal epileptiform activity | n/a              | n/a              | n/a                |
| Epilepsy                                     | Yes                 | Yes                 | Yes                  | Yes               | Yes               | Yes              | No                 |
| Microcephaly                                 | No                  | Learning difficulties (IQ 75) ADHD | Intellectual disability with severe language dysfunction | Acquired intellectual disability | Acquired intellectual disability | Learning difficulties | Acquired intellectual disability IQ 51 (with 10 years) Mild ataxia |
| Cognitive development                        | Mld intellectual disability ADHD |                       |                      |                   |                   |                   |                    |
| Neurological abnormalities                   | Clumsiness          | n/a                 | Ataxia, dyspraxia    | Ataxia            | Lower limb spasticity and ataxia | n/a              |                    |
| Paroxysmal hemiplegia with/without associated symptoms | Hemiplegia with sensory and visual disturbances, vomiting, and difficulties in finding words | Hemiparesis with altered mental status and vomiting | Monoparesis with asthenia, ataxia, somnolence, vomiting, and pallor | Hemiplegia with inability to speak, sensory and visual disturbances, and vomiting | Hemiplegia with photopsia, pallor, nausea, photophobia | n/a              | Hemiplegia including unilateral facial weakness |
| Associated headache                          | Yes                 | Yes                 | No                   | Yes               | Yes               | Yes              | No                 |
| Other paroxysmal events                      | PMKD                | n/a                 | n/a                  | PED               | n/a              | n/a              | EA with slurred speech |

(Continues)
The table shows our patient and other patients from the literature with Glut1 DS and paroxysmal hemiplegia (presenting as hemiplegic migraine or alternating hemiplegia of childhood). The affected gene SLC2A1 encodes the glucose transporter type 1 (GLUT1).

Our male, 16-year-old patient presented the following symptoms: at the age of 9 months he developed epileptic seizures and became seizure free under antiepileptic drugs with valproate (VPA). After VPA was discontinued, he again developed seizures, so VPA was reintroduced. Since the age of 6 years, he suffered from HMs. Attacks of HM occurred about 6 times a year without identifiable triggers. It usually started with blurred vision followed by hemiparesis. During an attack, hemiparesis spread from the leg to the arm and lasted for several hours. Sometimes he also had transient facial palsy. The affected body side changed between attacks. Additional symptoms were headache, vomiting, and difficulty finding words. Paracetamol, ibuprofen, and triptans had no effect on the symptoms.

Furthermore, the patient had difficulties in learning. He had also transient facial palsy. The affected body side changed between attacks. Additional symptoms were headache, vomiting, and difficulty finding words. Paracetamol, ibuprofen, and triptans had no effect on the symptoms.

At presentation, he had muscular hypotonia and clumsiness. Head circumference was on the 60th percentile. Family history revealed a inherited condition with low IQ.

Since the age of 16 years, he received methylphenidate with a moderate effect. Since the age of 10 years, he suffered from HMs. Attacks of HM occurred about 6 times a year without identifiable triggers. It usually started with blurred vision followed by hemiparesis. During an attack, hemiparesis spread from the leg to the arm and lasted for several hours. Sometimes he also had transient facial palsy. The affected body side changed between attacks. Additional symptoms were headache, vomiting, and difficulty finding words. Paracetamol, ibuprofen, and triptans had no effect on the symptoms.

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The asymptomatic parents declined segregation analysis, so we cannot determine whether it is inherited or de novo.

Further genes (ie, ATP1A2, ATP1A3, CACNA1A, NOTCH3, POLG, PRRT2, SCN1A, SLC1A3) as a possible cause of HM were examined in a genetic panel analysis and excluded other pathological variants.

As a result of the genetic findings, Glut1 DS was confirmed as the diagnosis. We dispensed with a cerebrospinal fluid puncture as the phenotype was suitable. Magnetic resonance imaging (MRI) showed no abnormalities except for an arachnoid cyst.

A KD was introduced on an outpatient basis. About 36 hours after the start of KD, our patient developed a paroxysmal dyskinetic movement storm. This was interrupted by sugary drinks. The second time, KD initiation was realized during an inpatient stay in our clinic. Again, the patient showed PNKD about 36 hours after the beginning of the diet (see Videos S1 and S2). During this time, the patient was fully conscious and complained of uncontrolled movements of the arms and legs, which would increase with targeted movements and improve when lying still in bed. During PNKD, the patient had a normal glucose serum level of 5.0 mmol/L (reference values, 3.9–5.5 mmol/L) and a low level of ketone bodies with 0.6 mmol/L (target range under KD, 3–5 mmol/L). After oral administration of 2.5 mg lorazepam, the dyskinesia slowly stopped. KD was continued. In the longer term, our patient benefited greatly from KD. The measured ketone bodies were usually in a range between 2.5 and 3.5 mmol/L. Within the 11-month follow-up, paroxysmal dyskinesia did not recur.

Under KD in the follow-up, he reported 2 episodes with attenuated symptoms of HM. One episode occurred when he had consumed more carbohydrates. The ketone bodies were not measured, but we assume that they were lower because of the diet mistake. The second attack occurred with a proven low blood ketone level of 1.2 mmol/L.

Therapy with VPA and methylphenidate was discontinued after KD was introduced. The intelligence test 6 months after the start of KD showed an unchanged intelligence quotient of 75, but the patient had a noticeable improvement in concentration and the results at school have improved by 1–2 levels. No further epileptic seizures or other paroxysmal events were reported during the 11-month follow-up after the start of KD.

**Literature Review**

The following questions arose in our case: Is HM a symptom already described in Glut1 DS, and how can we place it in context of the disease? Have central nervous effects been reported under KD in other patients as they occurred in our patient?

Few patients have been reported with HM and Glut1 DS (see Table 1). Furthermore, AHC has been described with Glut1 DS as cause of paroxysmal hemiplegia. Conversely, in a cohort of 23 patients with AHC, none of the 23 patients were shown to have the SLC2A1 mutation.

All patients with Glut1 DS and alternating hemiplegia, either classified as HM or AHC, presented with additional neurological symptoms such as developmental disorder, epilepsy or ataxia.

The underlying pathomechanism for HM in Glut1 DS is not well understood. Almuqbil and colleagues were able to show perfusion abnormalities in MRI/magnetic resonance angiography during paroxysmal hemiplegia in Glut1 DS. Pellegrin and colleagues found a focal electroencephalogram slowing contralateral to hemiparesis. Most likely hypometabolism of the central nervous system causes reversible hemiplegia in Glut1 DS. Alternatively, a causal disorder or dysregulation of the cerebral vessels is discussed.

Regarding adverse central nervous system effects under KD, we found only 1 case report. The reported patient had a complex neurological clinical picture and drug-resistant epilepsy of unclear etiology. She developed dystonia, ataxia, and chorea under KD, and her MRI showed bilateral symmetrical reversible hyperintensity of the putamen. Magnetic resonance spectroscopy showed a lactate peak in the basal ganglia and implicated a failure of aerobic energy metabolism. Metabolic diseases were excluded before the start of KD in this patient, but an underlying disease could be assumed.

No further reports of PxD triggered by KD were found, even in patients with Glut1 DS.

**Discussion**

We report on a patient with Glut1 DS who carries a SLC2A1 missense variant and has learning difficulties and epilepsy and HM as a leading symptom. Missense variants in SLC2A1 have been previously associated with a milder phenotype. This is in accordance with the nonclassical course of our patient.

Hemiplegic episodes in our patient followed the classical course of HM with aura and headache.

With this report, we want to increase awareness of HM within the Glut1 DS symptom complex because paroxysmal hemiplegia is a poorly known symptom of Glut1 DS, and there are few case reports (see Table 1).

The underlying mechanism is not yet well understood. Functional studies (eg, functional MRI, positron emission tomography–MRI) during such HM episodes could provide further insights. However, because of the fact that the occurrence of HM is not predictable, systematic investigations are difficult to realize.

In patients with Glut1 DS, HM is not an isolated symptom. All reported patients (see Table 1), as in our case, showed additional neurological symptoms. Early diagnosis of Glut1 DS is important considering that with KD an effective therapy is available and early onset significantly improves the prognosis of cognitive outcome. Glut1 DS should be considered as an important differential diagnosis in HM, especially when there is a combination of several neurological symptoms. We therefore recommend early testing for Glut1 DS in these patients if HM is not otherwise explained.
A positive effect of KD on HM in our patient has been shown. This is in accordance with the reports from the literature where KD or a modified Atkins diet have shown a positive effect on HM or AHC in patients with Glut1 DS (Table 1). As expected, no additional epileptic seizures occurred, and our patient showed an improvement of concentration and school performance. However, under low ketone levels, the recurrence of HM is possible. Therefore, we recommend keeping the level of ketone bodies >3 mmol/L. A modified Atkins diet results in lower blood ketone levels, and thus does not alleviate cerebral energy shortage as sufficiently as KD. In these patients, KD should be the preferred diet as it reaches higher ketone levels.

Of note, KD is based on hunger metabolism, and there are contraindications. The low-carbohydrate diet can lead to a vital risk of the patient with certain metabolic diseases. Therefore, fatty acid oxidation disorders, disorders of ketogenesis and ketolysis, disorders of gluconeogenesis, pyruvate carboxylase deficiency, and hyperinsulinism must be excluded before the onset of KD.

Epilepsy in our patient was treated with VPA before Glut1 DS was diagnosed, and no further seizures occurred under VPA with good tolerability. When Glut1 DS was diagnosed, we started KD. The combination therapy of VPA and KD is possible if regular check-ups are performed. However, it should be noted that Wong and colleagues showed an inhibition of the glucose transport velocity under VPA treatment in Glut1 DS erythrocytes. This suggests that VPA should be avoided in Glut1 DS. In our patient, VPA and methylphenidate were no longer necessary after the onset of KD.

PNKD is known to belong to the spectrum of Glut1 DS. However, in our patient this symptom had not occurred before and did not recur during follow-up but was twice provoked by the initiation of KD. During the second episode, we could not prove hypoglycemia, but keton levels were still low. PNKD could have been associated with a temporary shortage of energy in the basal ganglia when KD was introduced. Nevertheless, in patients with Glut1 DS, the KD should not be discontinued in this situation when contraindications are excluded. The positive long-term effects outweigh short-term side effects in these patients.

**Conclusion**

We would like to draw attention to paroxysmal hemiplegia presenting as HM or AHC as a symptom of Glut1 DS. KD is an established therapy for Glut1 DS to improve development and treat epilepsy. With our case study and the cases described in the literature (Table 1), we were able to show that in patients with Glut1 DS, KD is also effective in preventing HM.

In addition, we describe PNKD provoked reproducibly by the initiation of KD. PNKD did not occur in our patient before the initiation of KD and not with established KD. Because fasting is also a trigger for PNKD in patients without Glut1 DS, this symptomatology is not surprising. However, this is the first description of a patient who developed PNKD through the introduction of KD. In our case, PNKD can be interpreted as a consequence of the transition phase in which the brain switches from glucose to ketone bodies as the main energy source. This is probably indicating a transient energy shortage in the basal ganglia.

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**Author Roles**

(1) Research Project: A. Patient Care, B. Evaluation of Genetic Findings; (2) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

J.G.-A.: 1A, 2A
A.H.: 1B, 2B
R.A.J.: 1B, 2B
A.M.: 1A, 2B

**Disclosures**

**Ethical Compliance Statement:** The patient was treated at our university hospital. The consent for treatment was signed by the parents at the outpatient presentation and for inpatient admission as part of our hospital formalities. We have received the declaration of consent for the publication of the medical data and the video from both parents and the patient. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. We confirm that the approval of an institutional review board was not required for this work. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

**Video S1.** The video was recorded about 36 hours after the ketogenic diet was initiated and is from the second episode of paroxysmal, nonkinesigenic dyskinesia in our patient. The patient was lying on the bed when the dyskinesia started. There was no previous physical activity. The patient is asked to sit up, which is not possible. Then the patient is asked to turn on his back, which is also not possible.

**Video S2.** The video was recorded about 36 hours after the ketogenic diet was initiated and is from the second episode of paroxysmal, nonkinesigenic dyskinesia in our patient. The second video was taken about 10 minutes after the first video, when there was a slight spontaneous improvement of the paroxysmal, nonkinesigenic dyskinesia. The patient sits on the bed and is asked to stand up and then walk.