A Cause of Permanent Ketosis: GLUT-1 Deficiency

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Abstract GLUT-1-deficiency syndrome (GLUT1-DS; OMIM 606777) is a treatable metabolic disorder caused by a mutation of *SLC2A1* gene. The functional deficiency of the GLUT1 protein leads to an impaired glucose transport into the brain, resulting in neurologic disorders.

We report on a 6-month-old boy with preprandial malaises who was treated monthly by a sorcerer because of a permanent acetonemic odor. He subsequently developed pharmaco-resistant seizures with microcephaly and motor abnormalities. Metabolic explorations were unremarkable except for a fasting glucose test which revealed an abnormal increase of blood ketone bodies. At the age of 35 months, GLUT1-DS was diagnosed based on hypoglycorrachia with a decreased CSF to blood glucose ratio, and subsequent direct sequencing of the *SLC2A1* gene revealed a *de novo* heterozygous mutation, c.349A>T (p.Lys117X) on exon 4. It was noteworthy that the patient adapted to the deficient cerebral glucose transport by permanent ketone body production since early life. Excessive ketone body production in this patient provided an alternative energy substrate for his brain. We suggest a cerebral metabolic adaptation with upregulation of monocarboxylic acid transporter proteins (MCT1) at the blood–brain barrier provoked by neuroglycopenia and allowing ketone body utilization by the brain. This case illustrates that

GLUT1-DS should be considered in the differential diagnosis of permanent ketosis.

Introduction

Glucose-transporter type 1 (GLUT-1) is one of the most important transporters of glucose through the blood–brain barrier (Dwyer et al. 2002), selectively in brain at the capillary endothelium. GLUT-1-deficiency syndrome (GLUT1-DS; OMIM 606777), first described by De Vivo et al. in 1991 (De Vivo et al. 1991), is caused by mutations of the *SLC2A1* gene and results in inadequate glucose delivery to the brain (Seidner et al. 1998). Consecutive disturbed cerebral metabolism explains the main symptoms that are developmental delay with deceleration of head circumference, early-onset and pharmaco-resistant epilepsy, and movement disorders (Wang et al. 2005). Moreover, the phenotype spectrum of GLUT1-DS has considerably expanded over recent years making early diagnosis challenging. We report the surprising case of a toddler having spontaneous permanent ketosis, a clinical and biochemical symptom which could be considered as an indicator for early diagnosis of GLUT1-DS and thereby offering treatment option by ketogenic diet.

Case Report

A 6-month-old boy, who is the first child of French non-consanguineous parents, was treated monthly by a sorcerer, because his mother thought this treatment would help against an acetonemic odor. He was referred to a neurologist

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due to preprandial malaises with abnormal eye movements, loss of contact, and hypotonia of the head. Standard biological tests and an electroencephalogram were normal. Treatment by antiepileptic drugs had no success. Head circumference was in the reference range and cerebral MRI was normal at 8 months of age. A control electroencephalogram before eating revealed paroxysmic epileptiform discharges and generalized discharge with intermittent light stimulation.

Frequency of the preprandial malaises accelerated during the following months and psychomotor development was retarded. The boy walked at 21 months with frequent falls. Head circumference dropped under the third percentile of age. There was no hepatomegaly. A metabolic work-up including venous blood gas analysis, liver and renal function tests, plasma electrolytes, ammonia, lactate, uric acid, amino and organic acids, carnitine, and acylcarnitines was unremarkable. A 14 h fasting test revealed excessive ketone body production with moderate hypoglycemia at the end (2.61 mmol/L); 3-OH butyrate levels raised to 4,236 $\mu\text{mol/L}$ (normal value: 80–900 $\mu\text{mol/L}$) and acetoacetate raised to 2,809 $\mu\text{mol/L}$ (normal value 30–400 $\mu\text{mol/L}$). Amino acid analysis revealed decrease of plasma alanine levels at the end of the test (H0: 316 $\mu\text{mol/L}$; H14: 47 $\mu\text{mol/L}$; normal values: 177–333 $\mu\text{mol/L}$), in favor of effective gluconeogenesis.

At 35 months of age, hypoglycorrachia was observed (CSF glucose: 2.0 mmol/L, blood glucose: 4.5 mmol/L, CSF/blood glucose ratio: 0.44), suggestive of GLUT1 deficiency. Direct sequencing of the *SLC2A1* gene showed a de novo heterozygous mutation, c.349A>T (p.Lys117X) on exon 4. A ketogenic diet was started at diagnosis and helped to control the seizures.

On clinical assessment at the age of 6 years, his head circumference had regained the second percentile for age with normal height and weight. Motor development was moderately impaired in fine motor movements and he suffered from buccofacial dyspraxia.

With the ketogenic diet improving his clinical condition, and an understanding of the underlying disorder, the acetonemic odor is now accepted by his family.

Discussion

Our case illustrates the presence of spontaneous ketosis in a particular genetic condition: haploinsufficiency of the facilitative glucose transporter to the brain, GLUT1. To our knowledge, spontaneous ketosis has not been yet described in patients with GLUT1-DS (Leen et al. 2010; Pearson et al. 2013).

GLUT1 protein is encoded by the *SLC2A1* gene mapped to chromosome 1 (1p35.31.3) (Mueckler et al. 1985). Most of known *SLC2A1* gene mutations are de novo, although

autosomal dominant (Brockmann et al. 2001; Klepper et al. 2001) and autosomal recessive inheritance (Rotstein et al. 2010) can be found in affected families. As far as we know the mutation c.349A>T (p.Lys117X) on exon 4 we describe here has never been reported in the literature. Analysis of the patient's parents confirmed that this mutation occurred de novo.

Haploinsufficiency of GLUT1 protein leads to an impaired glucose transport into the brain. Classically, patients with GLUT1-DS have epilepsy, developmental delay, acquired microcephaly, cognitive impairment and varying degrees of spasticity, ataxia, and dystonia. Non-classic phenotypes have also been identified, which include exclusively movement disorders or neurologic manifestations (Pons et al. 2010; Wang et al. 2005). Our patient presented a typical phenotype at the time of diagnosis, with notably episodic chaotic eye movements (opsoclonus) well described in infants with GLUT1-DS (Pons et al. 2010). The symptoms were surprisingly associated and even preceded by a spontaneous permanent ketosis, revealed by the acetonemic odor, which was the first clinical sign. The mechanism by which spontaneous ketosis occurred in our patient is open to discussion.

Ketone bodies are essential alternative energy substrates to glucose during cerebral maturation and fasting state. In the fasting state, brain glycogen storage is exhausted within minutes. Amino acids and fat cannot be used by the brain for energy production. The delivery of ketone bodies (β -hydroxybutyrate and acetoacetate) from blood to brain requires the proton-coupled monocarboxylic acid transporter proteins (MCTs), principally MCT1. The brain's ability to switch from glucose oxidation toward ketone bodies requires a cerebral metabolic adaptation (Zhang et al. 2013) (Fig. 1a). In GLUT1-DS, ketogenic diet remains the treatment of choice, which provides ketone bodies generated from dietary fatty acid oxidation in the liver. Increasing blood ketone body concentrations lead to an upregulation of MCTs at the blood–brain barrier allowing ketone body utilization by the brain (Vannucci and Simpson 2003). This metabolic adaptation may be implicated in the efficacy of the ketogenic diet in GLUT1-DS, which was observed in our patient (Klepper 2008) (Fig. 1b).

Surprisingly, spontaneous ketogenesis occurred in our patient before introduction of the ketogenic diet and independently of a fasting state. The cerebral metabolic adaptation thus occurred before the clinical manifestations of this disorder. This observation has been observed before in an animal model. Marin-Valencia et al. have shown in a mouse GLUT-1-deficiency model that total blood ketone bodies were markedly increased with normal blood glucose concentrations in a non-fasting state. This implies that GLUT-1-deficiency mice exhibit ketosis that can constitute a metabolic adaptation (Marin-Valencia et al. 2012).

Fig. 1 Cerebral metabolic adaptation in physiological situation (a) and in GLUT1-DS treated with ketogenic diet (b)

Moreover, the onset of symptoms appeared in the toddler described here during weaning from breast milk. The higher fat content in breast milk might have had a protective role in GLUT1-DS, allowing excessive ketone body production. It has been observed before that suckling rats exhibit a relative ketosis maintained until weaning and facilitated by the high fat composition of maternal milk. The ketotic state allows utilization of non-glucose substrates, as glucose

supply is shortened in the immediate postnatal period due to interruption of the permanent materno-fetal glucose supply and an initially low mobilization of glycogen stores and low gluconeogenesis rate (Fung and Devaskar 2006). Furthermore, MCT1 expression has been demonstrated in abundance in brains of rats during this suckling period indicating the potential for regulation of expression of MCT1 by dietary factors (Leino et al. 1999). The potential

for regulation of expression of MCTs by dietary factors implying enhanced transcription and translation is supported by several studies principally based on electron microscopic brain studies using high-resolution immunocytochemical methods (Leino et al. 1999; Canis et al. 2009). Genetic factors modifying the availability of energy substrates as in the case of GLUT1-DS may in this sense influence MCT densities in different tissues in order to maintain cerebral metabolic homeostasis. This adaptation allows utilization of energy substrates in response to their availability that is closed to circulating blood levels and tissue monocarboxylate concentrations (glucose, lactate, pyruvate, and ketone bodies).

The synthesis of ketone bodies is enhanced in several situations: it represents a physiological adaptation to fasting states when glucose supply is shortened. Moreover, it occurs when beta-oxidation from fatty acids is upregulated with impaired utilization of acetyl-CoA in the Krebs cycle. This may be seen in cases of compromised glucose utilization, enhanced gluconeogenesis, or shortening of the Krebs cycle intermediate, oxaloacetate. Oxaloacetate depletion may on the other hand result in impaired gluconeogenesis, thus leading to further activation of fatty acid beta-oxidation. Inherited metabolic disorders resulting in ketotic states therefore include organic acidemias; glycogen storage disorders type 0, III, VI, and IX; mitochondrial respiratory chain disorders; and, if ketone body utilization is affected, ketolysis defects (Sass 2012; Saudubray 2012). Ketone bodies represent an important alternative energy substrate for cerebral metabolism, sparing amino acid utilization for gluconeogenesis. As the brain's demand for energy supply is a central regulating factor of ketone body production, glucose entry to the brain is a key element in the regulation of ketone body synthesis. As demonstrated by the patient described here, differential diagnosis of ketotic states should therefore include GLUT1-DS (Table 1).

Table 1 Differential diagnoses of spontaneous ketosis

Inborn errors of metabolism
– Glycogen storage disease types 0, III, IV, IX
– Gluconeogenesis defects
– Branched chain organic acidemias
– Mitochondrial respiratory chain disorders
– Defects of ketolysis
– GLUT-1-deficiency syndrome
Others
– Fasting states, catabolism
– Diabetes
– Corticosteroids
– Growth hormone deficiency
– Adrenal insufficiency

Conclusion

The patient reported here presented typical features of GLUT1-DS with an original adaptive spontaneous ketosis. Permanent ketotic state may be a key diagnostic element for GLUT1-DS.

Take Home Message

GLUT1-DS can present with spontaneous ketosis, reflecting a cerebral metabolic adaptation, and should be considered in the differential diagnosis of permanent ketosis.

Compliance with Ethics Guidelines

Conflict of Interest

Alexis Chenouard, Sandrine Vuillaumier-Barrot, Nathalie Seta, and Alice Kuster declare that they have no conflict of interest.

Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Details of the Contributions of Individual Authors

Patient investigation and care of the patient and planning: AK, AC.

Patient investigation (molecular analysis): SV-B, NS.

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