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Clinical Letter

Monocarboxylate transporter-1 deficiency results in severe metabolic acidosis with ketogenic diet in early onset absence epilepsy: Case report

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To the Editor

Ketogenic diet (KD) is commonly used in drug-resistant epilepsy, but is contraindicated in some metabolic disorders (i.e. defects in carnitine pathways and beta-oxidation) [1]. *SLC16A1* (OMIM 600682) encodes monocarboxylate transporter-1 (MCT1), involved in transmembrane transport of ketone bodies, lactate and pyruvate. Individuals with loss-of-function *SLC16A1* variants are prone to recurrent metabolic ketoacidosis [2]. Here, we present a girl with epilepsy and a likely pathogenic *SLC16A1* variant who developed severe metabolic acidosis on KD; MCT1 haploinsufficiency may explain her metabolic response and her epilepsy.

1. Patient

A 5-year-old girl had frequent absence seizures from age 2 years. Despite treatment with valproic acid, ethosuximide and levetiracetam, she had 40–60 witnessed absences per day, lasting 5–15 s. She was born at 25 weeks gestation (twin pregnancy), but had an uncomplicated neonatal course. Early developmental milestones were normal adjusting for prematurity, but neuropsychological assessment at 3 years found below average verbal comprehension and visual-spatial and working memory difficulties. Parents were non-consanguineous Sephardic Jewish, Moroccan and Hungarian descent; a twin brother was healthy and family history was non-contributory. She had borderline microcephaly (47 cm at 5 years of age) but small growth parameters overall with height and weight both at the 5th percentile; otherwise, general and neurologic examinations were normal. Brain MRI was normal, and EEG showed normal background with generalized epileptiform fragments and frequent electroclinical absence seizures. Comparative genomic hybridization microarray (4 × 180 K) and a 398-gene clinical epilepsy panel (Fulgent Diagnostics), which included *SLC2A1*, did not reveal pathogenic variants. Given her refractory epilepsy, she was admitted for KD initiation. Beforehand, she underwent a standard screening metabolic work-up [1], which did not reveal any concerning abnormalities; serum bicarbonate was 26.9 mM and urine ketones were negative.

On day 1 of admission, 2:1 ratio diet was started and the following morning increased to 3:1. However, overnight, she had vomiting episodes, and the following day was hypoglycemic (2.6 mM) with metabolic acidosis (pH 7.19, bicarbonate 12.8 mM, anion gap 22 mM; Fig. 1). Interestingly, her seizure frequency dramatically reduced to only 7 episodes that day. The following day, she had 6 more vomiting episodes, and laboratory results showed greater metabolic deterioration. KD was halted, and 5 % dextrose half-normal saline intravenous solution and bicarbonate replacement were started. The acidosis subsequently corrected, and she was discharged home the following day.

Encouraged by the seizure improvement in hospital, the parents

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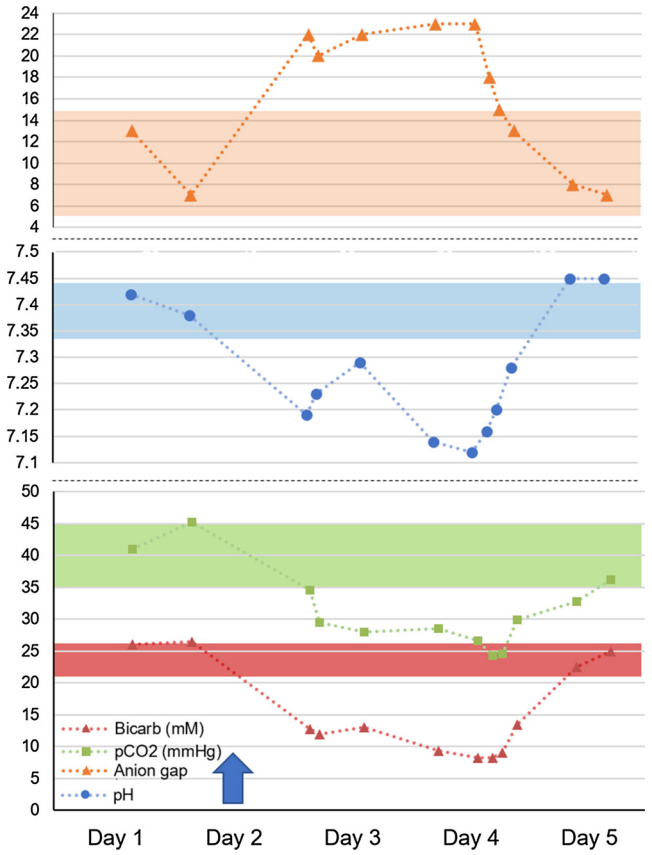

Fig. 1. Metabolic Deterioration with Ketogenic Diet Initiation. On day 1 of admission, pH, bicarbonate, anion gap and pCO_2 levels were normal. On day 2, a decompensation occurred following the increase of the KD ratio to 3:1 (blue arrow). There is a sudden drop in bicarbonate, pCO_2 and pH, and increase in anion gap. The diet was stopped on day 4, with subsequent normalization of these parameters by day 5. Normal ranges for bicarbonate (21 – 26 mM), pCO2 (35 – 45 mmHg), pH (7.34–7.44) and anion gap (5 – 15 mM) are indicated by the lightly shaded boxes (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

independently started the patient on KD protocol at home. The girl subsequently developed vomiting episodes and mild ketosis requiring short stays in the emergency department. The parents were advised to avoid KD or prolonged fasting in order to prevent further vomiting and ketosis episodes.

A 51-gene panel (sequencing and deletion/duplication analysis) for inborn metabolic disorders with hypoglycemia, hyperinsulinism or defective ketone metabolism (Blueprint Genetics) revealed a paternally-inherited, heterozygous, likely pathogenic *SLC16A1* frameshift variant (c.41dup, p. Asp15Argfs*34, previously described [2]).

2. Discussion

This girl has early onset absence epilepsy (EOAE) and developed severe metabolic acidosis with KD. She was subsequently found to carry a heterozygous frameshift *SLC16A1* variant which is predicted to result in premature MCT1 protein truncation; partial MCT1 deficiency accounts for her unexpected metabolic deterioration with KD, and may also be contributing to her epilepsy. The lack of symptoms in her father, who also carries the variant, may be because MCT1 deficiency appears to only produce symptoms in the context of other genetic or environmental factors [2].

The essential role of MCT1 in facilitation of trans-membrane diffusion of ketone bodies and lactate in hepatocytes and extrahepatic tissues was demonstrated in nine patients with *SLC16A1* variants; the clinical phenotype involved recurrent episodes of ketoacidosis with massive ketonuria and cyclical vomiting, occurring in times of catabolic stress or fasting [2]. Patients with biallelic pathogenic *SLC16A1* variants showed moderate intellectual disability [2]. Our patient had a heterozygous variant with a single base pair duplication of *SLC16A1*, causing a frameshift, leading to the protein truncation or nonsense decay; the same variant, when homozygous, causes profound ketoacidosis in association with moderate intellectual disability, microcephaly and congenital heart disease [2]. In our patient's case, severe ketoacidosis developed as a result of metabolic decompensation, which was induced by the KD. MCT1 deficiency should therefore be considered a contraindication for any low carbohydrate diet.

Only one patient has been reported with MCT1 deficiency and seizures, a girl with a homozygous *SLC16A1* pathogenic variant; unfortunately, no clinical information was given regarding epilepsy phenotype [2]. Nevertheless, there are mechanistic reasons to consider that *SLC16A1* pathogenic variants could be a cause of seizures, and specifically EOAE. A leading epilepsy genetics group previously hypothesized that deficiencies in MCT1 and other transporters involved in cerebral energy supply might cause EOAE [3]. They sequenced *SLC16A1*, and four other related transporter genes in 119 patients with EOAE or myoclonic atonic epilepsy. Although they did not identify any clearly pathogenic variants in any of the genes, the finding in our patient may now have confirmed their initial hypothesis.

As with another transporter-related genetic cause of epilepsy, GLUT1 deficiency, the most likely mechanism by which MCT1 deficiency might cause seizures is by depriving brain cells of fuel, namely ketone bodies and lactate. MCT1 is ubiquitous, but is prominently expressed on cerebral microvessels, playing a key role in the blood-brain barrier, by allowing transport of monocarboxylates [4]. With MCT1 deficiency, brain cells, which readily metabolize ketones, might not receive enough fuel. Human patients with mesial temporal lobe epilepsy, as well as animal models of the same disorder, have demonstrated local reduced MCT1 expression in the sclerotic regions of brain, leading to the hypothesis that MCT1 deficiency has an epileptogenic effect [4].

In summary, MCT1 deficiency should be a contraindication to the KD; our experience demonstrates that routine metabolic screening tests may not identify this condition, thus *SLC16A1* analysis should be included as part of pre-treatment screening. Though current guidelines consider inpatient initiation to be optional [1], there is the potential for rapid, severe clinical deterioration even when current pre-screening protocols are followed. Pathogenic variants in *SLC16A1* may also contribute to pathogenesis of EOAE and other forms of epilepsy, but further research is necessary to more thoroughly investigate this possibility.

Declaration of Competing Interest

None.

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