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Case Report

Rare cause of ketolysis: Monocarboxylate transporter 1 deficiency

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ABSTRACT

Background. Monocarboxylate transporter 1 (MCT1) deficiency (MIM #616095) is a relatively new identified cause of recurrent ketoacidosis triggered by fasting or infections. MCT1 was first described in 2014 by van Hasselt et al. to result from both homozygous and heterozygous mutations in the SLC16A1 gene. Patients with homozygous mutations are known to have a more severe phenotype with developmental delay and epilepsy. Thirteen patients with MCT1 deficiency with ketoacidosis have been reported in the literature to date.

Case. We describe a developmentally normal male patient with heterozygous missense variation in the SLC16A1 gene. Our patient who presented with cyclic vomiting and ketoacidosis episodes was found to have a heterozygous c.303T>G (p.Ile101Met) missense mutation.

Conclusions. It is crucial to take early preventive measures and to minimize the harmful effects of ketoacidotic episodes. MCT1 deficiency should be considered in the differential diagnosis of ketoacidosis in patients with normal SCOT and ACAT1 activities.

Key words: MCT1, ketoacidosis, ketone metabolism, vomiting.

Ketone metabolism provides an important energy source for many tissues during fasting.[1] Succinyl-CoA:3-oxoacid CoA transferase (SCOT), mitochondrial acetoacetyl-CoA thiolase (also known as β-ketothiolase or T2) and monocarboxylate transporter 1 (MCT1) deficiencies are ketone body utilisation and transporter defects and associated with severe intermittent ketoacidosis episodes.[1] Ketone bodies cross cell membranes by diffusion or the facilitator MCT1. The role of MCT1 in ketone metabolism is important, especially in catabolic stress.[2] The clinical findings occur especially in metabolic stress such as fasting and infections, from the first days of life to childhood.[1,3] The clinical features of the diseases are vomiting, dehydration, Kussmaul breathing and decreased consciousness. In general, specific organic acid excretion is detected in T2 deficiency, whereas there is no specific excretion in SCOT and MCT1 homozygous and heterozygous mutations in the *SLC16A1* gene encoding MCT1 in ketoacidotic patients with profound ketoacidosis.[3,4] The clinical features of monocarboxylate transporter-1 deficiency (MCT1D) are vomiting, severe ketoacidosis and ketotic hypoglycemia.[3] To our knowledge, a total of 13 patients (MCT1 deficiency with ketoacidosis) have been reported in the literature to date.[3,5-7] Here we report an infant with ketoacidosis and vomiting caused by a heterozygous mutation in the *SLC16A1* gene.

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Case Report

A two month and 20 day old male patient born to second degree consanguineous parents was referred to the pediatric metabolism department

due to repetitive vomiting and hypotonia. Prenatal and natal history was uneventful, with normal antenatal follow up. The patient began vomiting soon after birth. The first physical examination at the age of two months and 20 days revealed mild axial hypotonia and he was unable to hold his head. He only had esotropia of the right eye as a congenital malformation. No other dysmorphic features were noted. Laboratory findings of the patient were; venous blood pH 7.31, bicarbonate 18.6 mmol/L, BE -6.3 mmol/L, lactate 4.1 mmol/L. Blood ketone was measured as 5.2 mmol/l with a ketone strip. Plasma glucose was 89 mg/dl. Ammonia level was 179.68 μmol/l and 163.83 μmol/l. Significant urinary excretion of ketones was demonstrated. Liver transaminases and creatine kinase remained normal. Serum B12 level was determined as 262 pg/ml (RR: 197-771). The patient was not hypoglycemic. Serum lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) was normal. He was treated with high dextrose concentrations (continuous infusion of dextrose at 8 mg/kg/min) and sodium benzoate. Within the next few hours, the patient's venous blood findings were; pH 7.35, bicarbonate 22.3 mmol/L, BE -2.4, lactate 1.9 mmol/L. Post-treatment ammonia level was measured as 49.32 μmol/l. His quantitative blood aminoacid analysis was normal (glutamine and glycine were normal). Tandem-MS analysis revealed slightly elevated C3 carnitine (C3:3.94 mol/L RR: 0.08-1.77). Homocysteine was 4.32 μmol/L. In the urine organic acid analysis, 3 hydroxy butyric acid excretion had increased 24 times, methylmalonic acid excretion increased 4.6 times, succinic acid excretion increased 3.4 times more than the normal range. The patient was followed up and treated with a preliminary diagnosis of organic acidemia due to metabolic acidosis with ketosis, mild hyperamonemia, slightly elevated C3 and methylmalonic acid excretion. Molecular analysis was performed for methylmalonic aciduria (*MUT, MMAA, MMAB, MMACHC, MCEE, SUCLA, SUCLG1*) and found to be normal. The patient presented three times with vomiting and ketoacidosis episodes. Initial blood ketone levels measured by ketone strip were 5.4, 6.2, and 5.0 mmol/l in each episode, respectively. Serum ammonia levels were detected between the normal range except the first admission. Each acute episode of illness was managed with intravenous dextrose and sodium bicarbonate. Sodium benzoate treatment was not continued. The patient didn't have resistant ketoacidosis episodes and did not need dialysis. Echocardiographic findings were normal. During the follow-up, the developmental milestones gradually improved. When he was nine months old, his weight was 8 kg (-1.18 SDS) and height was 65 cm (-2.75 SDS). The most recent physical examination (including the neurological examination) was normal, except for esotropia and short stature (Fig. 2). Neuroimaging was not performed. He had three ketoacidosis episodes in five months and no symptoms between the acidosis episodes. His current age is one and half years and he has had no ketoacidosis episodes in the last ten months.

Whole Exome Sequencing (WES) analysis was performed. We found a heterozygous c.303T>G (p.Ile101Met) missense variant in exon 3 of the *SLC16A1* (NM_001166496.1) gene. IGV images of the mutation are shown in Figure 1. It was evaluated as a variant of unsignificant (VUS) in insilico predictive tools for the *SLC16A1* gene. We considered this change to be disease-causing in our patient based on the population data (low frequency in GnomAD population database), pathogenic computational predictions (DANN, M-CAP, MutationAccessor, MutationTaster, SIFT) and the clinical finding of ketoasidosis episodes. Segregation analysis was performed on the mother and father of the patient. The same mutation was found to be heterozygous in his father. It was learned that his father had a history of hospitalisation with three metabolic acidosis episodes in his childhood, and he did not have any problems after the age of seven. However, ketone levels during the episodes were unknown. A fasting test was not performed due to a lack of the patient's approval. MCT transport activity could not be performed due to technical incompetence.

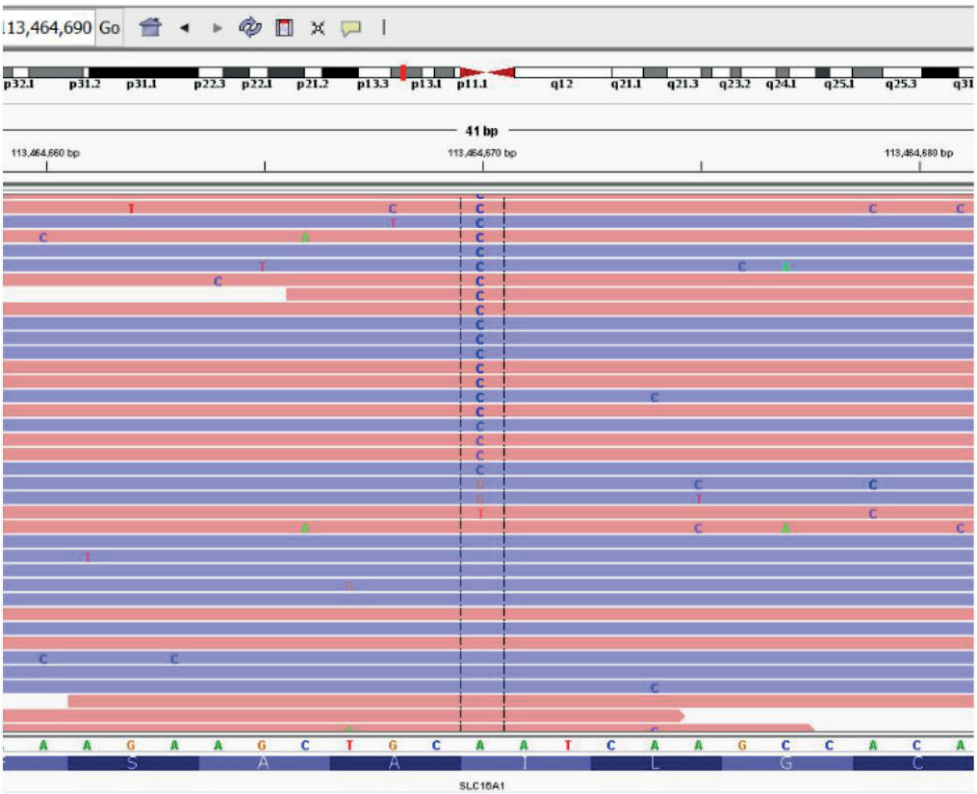

Fig. 1. IGV images of the SLC16A1 gene. c.303T>G (p.Ile101Met) missense variation detected by Whole Exome Sequencing.

Fig. 2. The nine months old male patient with MCT1 deficiency.

The primary aim of the patient's treatment was to prevent decompensation. The parents were informed about high glucose intake during states of metabolic stress such as infections and were warned about the avoidance of fasting.

Discussion

Mutations in the *SLC16A1* gene are associated with erythrocyte lactate transporter defect and monocarboxylate transporter 1 deficiency.[4,8] The MCT1 protein, is a proton-linked monocarboxylate transporter that catalyzes the rapid transport of many monocarboxylates, such as lactate, pyruvate, branched chain oxo acids derived from leucine, valine and isoleucine and the ketone bodies acetoacetate, beta-hydroxybutyrate and acetate across the plasma membrane.[9] Gain-of-function MCT1 promoter mutations have been shown to be associated with hyperinsulinism due to inducing SLC16A1

expression in beta cells.[10] It occurs due to the failure of cell-specific transcriptional silencing. Inactivating mutations in the SLC16A1 gene are associated with ketoacidosis episodes. Neurological problems such as developmental delay and epilepsy, and severe ketoacidosis episodes are more common in homozygous patients. In heterozygotes patients, normal development and normal blood pH and ketone values between episodes have been reported.[3,7]

MCT1 deficiency was first reported by van Hasselt et al. in 2014 as a cause of recurrent severe ketoacidosis induced by fasting or infections starting during infancy.[4] After identifying a homozygous frameshift mutation in a patient by targeted homozygous-region exome sequencing, they sequenced *SLC16A1* gene in 96 patients with ketoacidosis who were known to be normal for SCOT and ACAT1 enzymatic activities. They identified a total of nine patients with mutations in the MCT1, three homozygous and six heterozygous, including two siblings. They studied the effect of mutations in MCT1 on monocarboxylate transport. They found that the mutational status was correlated with MCT1 protein levels, transport capacity, and ketoacidosis severity. The mean lactate transport activity from heterozygous carriers, both symptomatic and asymptomatic, was significantly reduced. They reported that all patients (both homozygous and heterozygous) presented with bouts of ketoacidosis in their first years of life. Patients with homozygous mutations had a more severe phenotype with earlier onset of disease, more profound ketoacidosis, developmental delay and an increased prevalence of epilepsy. The frequency of the ketoacidosis episodes decreased over time with complete resolution after the age of seven years except ketonuria associated with mild infections in some of the patients.[4] van Hasselt et al.[4] reported that in the individuals with inactivating homozygous or heterozygous pathogenic variants in the SLC16A1 gene, hypoglycemia was seen infrequently. Heterozygous c.303T>G (p.Ile101Met) mutation in the *SLC16A1* gene was detected in our patient who presented with vomiting and ketoacidosis without hypoglycemia. Consistent with the literature our patient's blood pH values were within the normal range between attacks and hypoglycemia did not occur.

Balasubramaniam et al. described 2 half-siblings with MCT1D who had heterozygous nonsense mutations in the *SLC16A1* gene.[5] The asymptomatic heterozygous mother showed that additional triggers are needed for the development of ketoacidosis episodes. Segregation analysis was performed on our patient. A heterozygous mutation was detected in his father. We learned that he had acidosis attacks in his childhood, but we could not reach medical records.

Al-Khawaga et al.[6] described 28-month-old female patient with recurrent ketoacidosis and hypoglycemia who was found to have a homozygous pathogenic variant in the *SLC16A1* gene. The patient had seizures, and this was the first report of neuroimaging findings in MCT1D. The cranial MRI of the patient showed subependymal heterotopia and a specific signal alteration. The following and the last report of MCT1D was also about neuroimaging findings and was published by Nicolas-Jilwan et al.[7] MCT1, especially expressed in oligodendroglia, provides lactate delivery to neuronal cells. Lee et al.[11] reported that disruption of this transporter leads to axon damage and neuron loss in animal and cell culture models. It has also been shown that the MCT1 transporter is reduced in amyotrophic lateral sclerosis patients and mouse models.[11] This suggests a role for oligodendroglial MCT1 in the pathogenesis. In many studies, MCT defects are associated with neurodegeneration, epilepsy, cognitive impairment and metabolic disorders. This may explain the neurological deterioration in patients. In the literature, corpus callosum agenesis, T2 hyperintense signal abnormalities in basal ganglia, thalamus, dentate nucleus and hyperintense signal abnormalities in

cortical/subcortical white matter, U-fibers were reported.[6,7] We did not perform neuroimaging in our patient. However, further research is needed to elucidate this.

To the best of our knowledge, 13 cases (MCT1 deficiency with ketoacidosis) have been described in the literature. Hyperammonemia was not reported in any of the patients with MCT 1 deficiency. In our case, ammonia levels were normal without ammonia scavenger treatment in the follow-up. This may be clarified in further studies.

Our patient had short stature which has also been reported in the literature in a 10-year old patient with a heterozygous mutation of the MCT1 gene by van Hasselt et al.[4] We believe the cause of short stature in our patient to be familial, since his parents were also short. A longer follow-up period is required to assess short stature.

The c.303T>G (p.Ile101Met) variant in exon 3 of the *SLC16A1* gene is expected to cause the disease because it has a low frequency in GnomAD population database, has pathogenic computational predictions (DANN, M-CAP, MutationAccessor, MutationTaster, SIFT) and recurrent ketoacidosis finding. However, further functional studies are required to validate the genotype-phenotype correlation. Our case describes another heterozygous patient with MCT1 deficiency who had recurrent ketoacidosis and normal developmental milestones.

MCT1 deficiency should be considered in the differential diagnosis of ketoacidosis in patients with normal SCOT and ACAT1 activities. It is crucial to take early preventive measures and minimize the harmful effects of the ketoacidotic episodes.

Ethical approval

Written informed consent was obtained from the parents to publish this case report.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: AEB, ATÜ; data collection: AEB; analysis and interpretation of results: AEB, ATÜ; draft manuscript preparation: AEB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Morris AAM. Disorders of ketogenesis and ketolysis. In: Saudubray JM, Baumgartner M, Walter J (eds). Inborn Metabolic Diseases (6th ed). Berlin, Heidelberg: Springer, 2016: 217-222. https://doi.org/10.1007/978-3-642-15720-2_14
2. Halestrap AP. The SLC16 gene family - structure, role and regulation in health and disease. Mol Aspects Med 2013; 34: 337-349. https://doi.org/10.1016/j.mam.2012.05.003
3. van Hasselt PM, Ferdinandusse S, Monroe GR, et al. Monocarboxylate transporter 1 deficiency and ketone utilization. N Engl J Med 2014; 371: 1900-1907. https://doi.org/10.1056/NEJMoa1407778
4. Mitchell GA, Fukao T. Inborn errors of ketone body metabolism. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds). The Metabolic and Molecular Basis of Inherited Disease. New York: McGraw-Hill, 2001: 2327-2356.
5. Balasubramaniam S, Lewis B, Greed L, et al. Heterozygous Monocarboxylate Transporter 1 (MCT1, SLC16A1) deficiency as a cause of recurrent ketoacidosis. JIMD Rep 2016; 29: 33-38. https://doi.org/10.1007/8904_2015_519
6. Al-Khawaga S, AlRayahi J, Khan F, et al. A SLC16A1 mutation in an infant with ketoacidosis and neuroimaging assessment: expanding the clinical spectrum of MCT1 deficiency. Front Pediatr 2019; 7: 299. https://doi.org/10.3389/fped.2019.00299

7. Nicolas-Jilwan M, Medlej R, Sulaiman RA, AlSayed M. The neuroimaging findings of monocarboxylate transporter 1 deficiency. Neuroradiology 2020; 62: 891-894. https://doi.org/10.1007/s00234-020-02435-7

8. Merezhinskaya N, Fishbein WN, Davis JI, Foellmer JW. Mutations in MCT1 cDNA in patients with symptomatic deficiency in lactate transport. Muscle Nerve 2000; 23: 90-97. https://doi.org/10.1002/(SICI)1097-4598(200001)23:1<90::AID-MUS12>3.0.CO;2-M

9. Martinez BA. Lactate-starved neurons in ALS. Dis Model Mech 2012; 5: 711-712. https://doi.org/10.1242/dmm.010892

10. Otonkoski T, Jiao H, Kaminen-Ahola N, et al. Physical exercise-induced hypoglycemia caused by failed silencing of monocarboxylate transporter 1 in pancreatic beta cells. Am J Hum Genet 2007; 81: 467-474. https://doi.org/10.1086/520960

11. Lee Y, Morrison BM, Li Y, et al. Oligodendroglia metabolically support axons and contribute to neurodegeneration. Nature 2012; 487: 443-448. https://doi.org/10.1038/nature11314