Methylmalonyl CoA epimerase (MCE, another name being methylmalonyl-coA racemase) catalyzes the transformation of (S)-methylmalonyl-CoA to (R)-methylmalonyl-CoA in the propionyl-CoA to succinyl-CoA pathway. The pathway is responsible for the degradation of branched chain amino acids, odd chain-length fatty acids, and other metabolites. MCE is encoded in humans by the MCEE gene located on chromosome 2p13.3. MCEE is a small gene containing 4 exons.

The first MCE deficiency (OMIM 251120) case published in 2006 was followed by a small number of publications.\textsuperscript{1-7} The clinical spectrum of MCE deficiency ranges from asymptomatic to life-threatening metabolic decompensation attacks. Two cases with neurological findings from the cases described in the literature were also affected by a second inherited disorder, sepiapterin reductase (SR) deficiency.\textsuperscript{2,6}

Herein we report a patient diagnosed with MCE deficiency with recurrent acute metabolic ketoacidosis attacks and moderate MMA-uria that persisted in periods without decompensation. At presentation, organic acid profiles were dominated by increased 3 hydroxybutyrate.

Conclusions. 3-Oxothiolase deficiency as a main ketolysis defects disorder was initially suspected. However, the subsequently repeated organic acid analyses demonstrated mild and persistent elevation of methylmalonic acid. This report provides a new phenotype of the clinical and biochemical characterization of MCE deficiency.

Key words: methylmalonyl-CoA epimerase, methylmalonic aciduria, ketosis.

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pCO₂ 17 mm Hg, anion gap 20 mmol/L, accompanied by strong ketonemia in fresh capillary whole blood (5.2 mg/dl) and ketonuria (100 mg/dl). Glycemia was normal. There was no hyperlactatemia, hyperammonemia. High glucose content fluid (10 - 12 mg/kg per minute) was given to the patient in metabolic decompensation to meet his energy needs. When blood glucose was greater than 150 mg/dL, IV insulin infusion (began at 0.01 units/kg per hour and titrated according to blood sugar levels) was instituted to promote anabolism. Blood glucose was maintained between 100 and 150 mg/dL. Metabolic investigation results were consistent with a ketolysis defect with a large increase in urine 3-hydroxy-butyrate (25200 mmol/mol Creatine; N < 11) and acylcarnitine profiles were normal. Increased urinary 3-hydroxy-butyrate addressed the diagnosis of acetyl-coa acetyltransferase 1 (ACAT1) deficiency. Unexpectedly, no mutation was detected in ACAT1 gene analysis. Three months after his first decompensation attack, he had the second one with ketoacidosis. Blood β-Ketone (Beta-Hydroxybutyrate) in fresh capillary whole blood from the fingertip was elevated (6.4 mg/dl). MMA was still not detected in his urine organic acid analysis. But unlike the first attack acylcarnitine profile showed an elevation of C3 (propionyl) carnitine (7.7 μmol/L; N < 6). His plasma homocysteine level was normal (5.2 μmol/L, N: 5 – 15). No mutation was defined in the MUT gene analysis that was studied to exclude methylmalonic aciduria. During his follow-up, twelve assessments were performed, with results ranging from undetectable (twice during metabolic decompensation) to 1234 mmol/mol creatine, with a mean of 258 and a median of 145. The brain MRI and echocardiography were normal.

With these findings, as methylmalonic aciduria is present in several inborn errors of metabolism affecting different steps of cobalamin pathways a clinical whole-genome sequencing was ensued. In the MCEE gene data analysis performed due to persistent methylmalonic acid excretion in between attack periods, a previously described homozygous nonsense mutation (c.139C>T) was identified and validated by the Sanger sequencing. Following the initial acute decompensation, he was treated with carnitine supplementation (50-100mg/kg/day). Protein restriction in the diet was recommended only during metabolic decompensation periods. Now at age seven and half years, growth and development are completely normal. The patient has successful academic results in school.

Urine organic acids analysis was planned for parents and both siblings. His eleven year old brother (V-1) had a meningomyelocele which had been operated on. He has a neurogenic bladder and is treated with clean intermittent catheterization three or four times a day. He has never had a decompensation attack despite surgery for the meningomyelocele. He has normal growth parameters and is successful in school. His sister (V-3) had normal growth and development and had no decompensation attack. Urine organic acids indicated that the older brother with neurogenic bladder and younger sister also have methylmalonic aciduria, 888 mmol/mol creatinine, and 3 mmol/mol creatinine, respectively. The family did not allow genetic studies from the two siblings.

Informed consent was obtained from the parents of the patient for publication of this case.
Discussion

After the first case was described in 2006, a small number of cases have been reported so far, and the clinical presentations are very diverse.\textsuperscript{1-7} Previously reported three patients presented with an acute metabolic decompensation with acidosis but severe ketonemia was not described in these patients (Table I). Although severe metabolic ketoacidosis was detected in both metabolic decompensation episodes of the case, ammonia and glucose levels were found to be normal. So this report provides a new phenotype of the clinical and biochemical characterization of MCE deficiency via mimicking ketolysis defects. As in the case reported by Abily-Donval et al.,\textsuperscript{5} in our case also, no MMA was detected in two decompensation attacks. This finding reveals the importance of organic acid analysis in the periods between metabolic decompensation attacks on follow-up.

An increase in creatine kinase was reported during an attack in a case presented previously.\textsuperscript{4} No increase in muscle enzymes were detected in our patient’s decompensation attacks and on follow-up.

Neurologic involvement was described in five cases.\textsuperscript{2,3,5-7} Two of them were diagnosed with a second inherited metabolism disorder, SR deficiency.\textsuperscript{2,6} SR deficiency is an autosomal recessive inherited defect in the biosynthesis of tetrahydrobiopterin. The SPR gene is also located on chromosome 2, like the MCEE gene. SR deficiency is characterized by dystonia, axial hypotonia, oculogyric crises, and delays in motor and cognitive development. Considering the coexistence of these two diseases in two cases in the literature, contiguous gene deletion syndrome was excluded. Because the SPR gene and MCEE gene mutations in both families were missense mutations. The evaluation of SR deficiency was not mentioned in the other two patients with neurological findings to confirm the exclusive association with MCE deficiency.\textsuperscript{3,5}

In the MCEE gene analyses of 9 previously reported patients listed in Table I, c.139C>T was shown in 14 alleles. c.139C>T variation is a stop codon mutation.\textsuperscript{1-7} Our case was also homozygous for the missense mutation c.139C>T. We did not make any evaluation in terms of vitamin B12 responsiveness because previous cases were unresponsive in the literature.\textsuperscript{2,5,7} There is no consensus on dietary protein restriction or a normal protein diet yet. Examples of both applications have been reported in the cases in the literature.\textsuperscript{1,2,5} To achieve this unity of decision, there is a need to increase the experiences and cases about MCE deficiency. Our case was not given a protein-restricted diet on follow-up, except during metabolic decompensation attacks.

In summary, we have reported a new case of the rare disease MCE deficiency, presenting with strong ketosis. So we described a new biochemical phenotype for MCE deficiency. We emphasize the importance of the metabolic sample during the attack, as well as the sample in between the attack period on follow-up.

Ethical approval

Informed consent was obtained from the parents of the patient for publication of this case.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: HY and SKU; data collection: EC, SH and HO; analysis and interpretation of results: HY, MÇ; draft manuscript preparation: HY. 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.
| Table I. Clinical, biochemical and molecular findings. |
|-------------------------------------------------------|
| Patients     | P1 | P2 (P1S) | P3 | P4 (P3S) | P5 | P6 | P7 | P8 | P9 | Case |
| References   | 1  | 1        | 2  | 3         | 3  | 5  | 5  | 6  | 7  | Yes  |
| Sepiapterine | Yes|          | Yes| Non communicated | Yes|    | Yes| No | No | No   |
| Reductase    |    |          |    |           |    |    |    |    |    |      |
| Deficiency   |    |          |    |           |    |    |    |    |    |      |
| MCE Deficiency | 13 months | 14 years (Asymptomatic) | 16 years (Asymptomatic) | 3 years | 5 years | 5 years | 2 years | 78 years | 3.5 years |
| Diagnosis age | Only before ventriculoperitoneal shunt due to hydrocephalus | Axial hypotonia, anormal eye movements, wheeled chair | No | Dysarthria, deteriorated motor function, spastic paraparesis, ataxia | No | Attentional difficulties, language development delay | Psychomotor development retardation, Spasticity | No |
| Neurological Impairment |    |          |    |           |    |    |    |    |    |      |
| Acute Metabolic Acidosis | Yes | No | No | No | No | Yes | Yes | No | No | Yes |
| Ketonuria     | No | No | No | No | No | Yes | Yes | No | Non communicated | Yes |
| Urinary MMA (Decompensation) (μmol/mmol Creatinine) | 180-1456 | No attack | No attack | No attack | 53 | Not detected | No attack | Not detected |
| Urinary MMA (μmol/mmol Creatinine) | 180-1456 | 95-1400 | 60 | 1400 | 621 | 47-121 | 18-212 | 1175 | 5.5-60 | 0-1234 |
| C3 (μmol/L) | 21.6 (<0.58) | No attack | 7.7 |
| (Decompensation) |    |          |    |
| C3 (μmol/L) | 1.53-5.82 | Unmeasured | 13 | N-3.7 |    |
| CK (IU/L) | 498-3062 | Unmeasured | No attack | 74 | 5.2 |
| HCY (μmol/L) | 17-32 | Normal | Protein restriction in attack | 8.3 |
| (Decompensation) |    |          |    |      |
| HCY (μmol/L) | Non communucated | Protein restriction in attack |      |
| Diet | Normoprotein restricted diet | Protein restricted diet | Non |
|        | | | communucated Protein restriction in attack |

CK: creatin kinase, HCY: homocysteine, MCE: methylmalonyl CoA epimerase, MMA: methylmalonic acid
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