

## Case Report

# Hypoglycemic Coma in a Young Girl: First Case of Medium Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency Identified in Kuwait

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Kuwait Medical Journal 2005, 37 (1): 50-53

**ABSTRACT**

Medium-chain acyl CoA dehydrogenase (MCAD) deficiency is the commonest inborn error of fatty acid oxidation. Affected children usually present within the first two years of life with recurrent episodes of hypoketotic hypoglycemia and lethargy with high risk of mortality and morbidity. We describe a two-year old girl who presented with hypoglycemic hypoketotic coma due

to MCAD and we describe the investigative work-up that led to the diagnosis. Our aim is to increase awareness of this disorder and to emphasize the need for prompt diagnosis and management. This is the first case of MCAD deficiency identified in Kuwait and we believe that this condition may be under-diagnosed.

**KEYWORDS:** children, fatty acid oxidation disorders, hypoglycemic hypoketotic, inborn errors of metabolism

**INTRODUCTION**

At times of stress or fasting, mitochondrial fatty acid oxidation becomes a major source of energy production. Genetic defects of mitochondrial fatty acid oxidation are an important group of inborn errors of metabolism (IEM) in which mitochondrial energy output is impaired and subsequently could lead to severe metabolic disturbances, hypoglycemia, encephalopathy, cardiomyopathy, myopathy or sudden infant or child death. Since their first recognition in 1973, altogether ten disorders of mitochondrial fatty acid oxidation and ketogenesis have been defined<sup>[1]</sup>.

MCAD deficiency, first described in 1982-1983<sup>[1,2]</sup>, is the commonest fatty acid oxidation defect accounting for a prevalence of about 1:10,000 amongst the population<sup>[3,4]</sup>. Like all fatty acid oxidation disorders, inheritance is autosomal recessive. The gene is on chromosome 1 and a point mutation A985G accounts for more than 90% of the alleles in MCAD deficient patients<sup>[1,3,5,6]</sup>. The enzyme MCAD catalyzes the initial step of mitochondrial  $\beta$ -oxidation of medium-chain fatty acids of C4 to C12 units in length<sup>[4]</sup>.

The clinical presentation of MCAD deficiency is typically a life-threatening episode of hypoketotic hypoglycemic encephalopathic coma, often Reye-like in its features, arising in association with a period of prolonged fasting during intercurrent illness. Undiagnosed, it has a high mortality rate of 20-25% during the initial acute episode and among survivors, 37% have neurodevelopmental problems<sup>[7]</sup>.

The first episode may be immediately fatal resembling sudden infant death. Prompt recognition is essential since once diagnosis has been made, the episodes are easily preventable by avoidance of fasting and simple instructions<sup>[1,3,8]</sup>.

We present this case of a young girl with MCAD deficiency to increase awareness of fatty acid oxidation disorders and to highlight the investigative steps that have led to a quick diagnosis. To the best of our knowledge this is the first report of MCAD deficiency from Kuwait.

**CASE REPORT**

A previously healthy, two-year-old non-Kuwaiti girl was found unarousable at 9:30 in the morning. In the hospital, one hour later, she was unresponsive with a Glasgow Coma Scale of six. She developed a brief tonic-clonic seizure and was given diazepam suppository. Blood sugar was checked by glucometer and found to be 1.1 mmol/L. An intravenous (IV) bolus of 10% dextrose 2.5 ml/kg was given followed by a continuous infusion and blood sugar went up to 2.6 mmol/L and then to 14.5 mmol/L.

Further review of the history showed that the child had taken her last meal, which was smaller than her usual intake, at 8 pm the previous night. There was a history of mild runny nose and cough of two days duration without fever, vomiting or diarrhea. History was also negative for possible drug intake or head trauma. She was the 3<sup>rd</sup> child, among four children, born to healthy consanguineous

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**Table 1**

Results of blood sample investigations

Investigations collected one hour after correction of a blood sugar of 1.1 mmol/L- all samples were collected simultaneously:\*

- Blood ketones (3 OH butyrate + acetoacetate)= 0.14 mmol/L (normal fasting 15 hrs: 0.1-2.1)
  - Free fatty acids 2175 umol/L(n = 130-445)  
Free fatty acid/ketone ratio 15 (normal <1)
  - Pyruvate 182 umol/L(n = 41-67) - Lactate/Pyruvate ratio 13.7 (normal).
  - Blood amino acids normal.
  - Total carnitine 20 umol/L(n = 43-65) - Free carnitine 13 umol/L (n = 30-50)
  - Serum cortisol 1255 nmol/L(normal fasting >400 nmol/L)
  - Serum Insulin <1.2 mu/L
  - Acylcarnitines by tandem mass spectrometry MS/MS (Blood spot on filter paper sent to Neo Gen lab, USA): 'significant elevation of octanoyl carnitine (C8) and milder elevation of C6 and C10. Interpretation: Profile of Medium-chain acyl Co A dehydrogenase deficiency'
- DNA analysis performed using polymerase chain reaction (Neo Gen lab) showed no copies of the common MCAD mutations A985G or C198T.
- Urine organic acid by GC/MS done by Cerba lab, France:
- |                         |                            | <u>normal</u> |
|-------------------------|----------------------------|---------------|
| Lactic acid             | : 20umol/mmol creatinine   | <76           |
| 4-OH-phenylpyruvic acid | : 9 umol/mmol creatinine   | Not detected  |
| Adipic acid             | : 164 umol/mmol creatinine | <11           |
| Suberic acid            | : 98 umol/mmol creatinine  | <3            |
| Sebacic acid            | : 31 umol/mmol creatinine  | Not detected  |
| 3 hydroxy sebacic acid  | : 6 umol/mmol creatinine   | Not detected  |
| Hexanoyl glycine        | : 25                       | Not detected  |
| Suberyl glycine         | : 114                      | Not detected  |

Interpretation: Profile compatible with Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency.

\*Apart for the acylcarnitines levels, all results arrived after discharge.

parents. Her elder sister and her younger brother were healthy. However, an elder brother had a history of birth asphyxia and global developmental delay. Physical examination showed a child with normal growth parameters, namely, weight, height and head circumference on the 10th centile. She was unconscious, but responsive to painful stimuli. She was afebrile and there was no respiratory distress. Oxygen saturation was 95% on room air. Heart rate was 140/min, respiratory rate was 20/min and BP was 80/50 mmHg. Pupils were constricted, equal, round and reactive. She was hypotonic. DTRs were present and plantar responses were down going. Examination of the respiratory and cardiovascular systems was normal. Liver was enlarged five centimeters below costal margin. Skin color was normal. There was no evidence of trauma or focal neurological deficits. Repeat blood glucose revealed a level of 4.5 mmol/L. She had not passed urine since bedtime; urine was immediately obtained by bladder catheterization, and was found to be negative for

ketones. The rest of the urine was saved for further studies. In view of the non-ketotic hypoglycemia, an inborn error of fatty acid oxidation was suspected and in addition to the usual basic investigations, samples for a metabolic work-up were immediately collected. Management was basically supportive and included intravenous drip of glucose providing approximately 6 mg/kg/min. To cover for the possibilities of meningitis or encephalitis, intravenous cephalexin and acyclovir were started.

Further laboratory studies were as follows: pH 7.26, HCO<sub>3</sub> 14.5 mmol/L, base excess -10.9 mmol/L, hemoglobin 102 g/L, WBCs 19.2x10<sup>9</sup>/L, platelets 322x10<sup>9</sup>/L, glucose 5 mmol/L, sodium 136 mmol/L, potassium 3.8 mmol/L, chloride 105.9 mmol/L, ammonia 102 umol/L (normal 15-32umol/L), lactate 2.5 mmol/L (normal 0.8-1.5), alanine aminotransferase (ALT) 29 u/L, alkaline phosphatase 239 u/L, bilirubin 5 umol/L, albumin 41 g/L. Urea, creatinine, calcium, magnesium, and phosphate levels were normal as well as the urinalysis that confirmed the absence of ketones. Blood ammonia, repeated four hours after admission was 52 umol/L and was normal thereafter. An electrocardiogram, computed tomographic scan of the head and echocardiogram were normal. Uric acid level, done on second day of admission was 378 (normal value 155-357 umol/L). Result of urine toxicology study was negative. Cultures of throat, urine and blood were sterile. Results that were received later are presented in Table 1.

After admission, the child remained in a semi-conscious state for seven hours, despite correction of her blood sugar. Thereafter, she slowly began to regain consciousness and was, more or less, able to sit up in bed by the evening and to have a snack. Blood glucose levels had remained stable with a continuous infusion of dextrose. Her mental status and tone continued to improve progressively and she was back to her usual state by next morning. By noon, she was eating well and the IV drip was safely discontinued. On the fourth day, the result of acylcarnitines (Neo Gen lab, USA) was available disclosing the diagnosis of MCAD deficiency (Table 1). She was put on a high carbohydrate, low fat diet. Parents were instructed never to let her fast longer than 8-10 hours with particular care to be taken during intercurrent illness. She was given an emergency dietary protocol to use during such periods and another paper that states the diagnosis and details the emergency management protocol that should be carried out if she presented at any time for medical treatment. Treatment with L-carnitine 100 mg/kg/d was initiated and she was discharged the same day.

At present, one and half years after diagnosis, she is doing quite well, has normal growth, no hepatomegaly, normal mentality and neurodevelopmental examination. Her three siblings were checked for MCAD deficiency by tandem mass spectrometry and were found to be normal.

## DISCUSSION

A child in coma often presents a challenge because the differential diagnosis is wide and immediate action is critical. Important history points should focus on previous health state, triggering events, medications, head trauma, infection or drug/toxin ingestion as well as family history. In our case, it became immediately known that she had severe hypoglycemia. The next diagnostic step was to quickly obtain a urine sample, a step frequently missed. Urine was instantly available for checking ketones and was frozen for organic acid assay and relevant blood samples were collected.

The clinical features in our patient were typical of MCAD deficiency. This disorder usually reveals itself for the first time in children between six months to two years and the usual situation follows a fasting period of 12 hours or more as a consequence of an intercurrent infection<sup>[1,3,6]</sup>. Our patient, 2.2 years of age, presented in a metabolic crisis triggered by a mild upper respiratory infection associated with a small pre-bedtime dinner and a long period of fasting (~13.5 hours). The episode in MCAD deficiency may present with lethargy, seizures and progresses rapidly to coma<sup>[3, 4, 6]</sup>. Hepatomegaly is usually present during the acute illness and patients are often hypoglycemic, non ketotic or with low to moderate ketones<sup>[1,6]</sup>. Due to the build up of toxic metabolites in MCAD deficiency, patients do not regain consciousness immediately after correction of hypoglycemia, with a time lag till full recovery takes place<sup>[1]</sup>.

The patient had metabolic acidosis, hyperammonemia and mild elevation of blood lactic and uric acid levels. Such biochemical features are well recognized with this disorder<sup>[1,3]</sup>. Another important feature during the acute episodes is the intense catabolic state reflected in the high free fatty acid levels, which the liver is unable to utilize<sup>[9]</sup>. Our patient, indeed, had a very high level of free fatty acids.

Medium chain dicarboxylic aciduria is the hallmark of the urine organic acid profile. During the acute phase, large amounts of dicarboxylic acids (adipic, suberic and sebacic) are excreted in the urine in addition to glycine conjugates of hexanoic and suberic acids, which are diagnostic in MCAD deficiency. After the acute phase, the urine

organic acid profile becomes normal<sup>[3]</sup>.

The accumulating medium-chain metabolites form esters with carnitine resulting in low plasma free carnitine levels and elevated acylcarnitines (octanoyl and hexanoyl carnitine). The profile of acylcarnitines in plasma, collected on filter paper and measured by tandem mass spectrometry, is unique and specific for MCAD deficiency, and provides rapid diagnosis both during the acute phase and when the patient is well<sup>[1,3,6]</sup>. DNA analysis performed in Neo Gen laboratory showed no copies of the common MCAD mutations (A985G or C198T) that account for more than 90% of the mutant MCAD genes causing this disorder in the white population<sup>[6]</sup>, indicating that she must be having one of the rare mutations.

When no samples have been collected at the time of the acute episode or the results are inconclusive, diagnosis of MCAD deficiency may be achieved by complex in-vitro studies of fatty acid oxidation or by direct assay of enzyme activity on cultured fibroblasts<sup>[10]</sup>.

The differential diagnosis includes adrenal insufficiency, which was ruled out. Additionally, the hypoglycemia in that condition is usually ketotic. Hyperinsulinism is another important cause to consider during a hypoketotic hypoglycemic event. In this condition, a very high glucose infusion rate (~12 mg/kg/min) is needed to correct and maintain the blood glucose within normal values. The serum insulin level was not elevated in our case and was appropriate for her blood glucose level. Finally, the markedly elevated level of free fatty acids indicated intense lipolysis, a process that would not occur in the presence of insulin<sup>[10]</sup>.

The hallmark of treatment is avoidance of fasting for more than ten hours. Extreme care is needed during intercurrent illness when a frequent intake of a high carbohydrate, fat restricted diet should be taken. Refusal of intake, vomiting or any signs of lethargy should indicate immediate hospital admission for intravenous high glucose intake and monitoring. L- carnitine is prescribed in MCAD deficiency to replenish the low free carnitine levels and to bind with toxic fatty acid oxidation intermediates, facilitating their urinary excretion<sup>[1,3,6]</sup>.

The Saudi experience<sup>[11]</sup>, is in keeping with others that MCAD deficiency is the commonest of the fatty acid oxidation disorders. Our patient is the first case identified in Kuwait, and since other fatty acid oxidation disorders, mostly very-long chain acyl CoA dehydrogenase deficiency, have been detected locally, a question, therefore, arises that MCAD deficiency may be under-diagnosed.

**ACKNOWLEDGMENT**

The authors would like to thank Dr Aravinda Rao and Dr Girish Y, Biochemistry and Hormone Laboratory, Sabah Hospital, for their help in organizing and performing the laboratory investigations. The authors also extend their appreciation to Dr Mohamed Zaki, Dr KC Aboobacker and Dr Zaidan Al-Mazidi for their valuable comments.

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