Intensive Care Med (2003) 29:1594–1597
DOI 10.1007/s00134-003-1871-3

BRIEF REPORT

F. Feillet
G Steinmann
C. Vianey-Saban
C. de Chillou
N. Sadoul
E. Lefebvre
M. Vidailhet
P. E. Bollaert

Adult presentation of MCAD deficiency revealed by coma and severe arrythmias

Received: 8 January 2003
Accepted: 23 May 2003
Published online: 1 August 2003

F. Feillet (✉) · M. Vidailhet
Service de Réanimation Médicale Pédiatrique,
Hôpital d'Enfants,
CHU Brabois, Allée du Morvan,
Vandoeuvre les Nancy, 54500 Nancy, France
e-mail: f.feillet@chu-nancy.fr
Tel.: +33-3-83154615
Fax: +33-3-83154529

G. Steinmann · P. E. Bollaert
Service de Réanimation Médicale Polyvalente,
Hôpital Central, Nancy, France

C. Vianey-Saban
Service de Biochimie Pédiatrique,
Hôpital Debrousse, France, France

C. de Chillou · N. Sadoul
Département de Cardiologie,
Hôpital Brabois Adulte,
Nancy, France

E. Lefebvre
Laboratoire de Biochimie Pédiatrique,
Hôpital d'Enfants, Nancy, France

Abstract We report the case of a 33-year-old man who presented with headaches and vomiting. Soon after admission he became drowsy and agitated, developed ventricular tachycardia and his neurological state worsened (Glasgow coma score 6). Blood analysis showed respiratory alkalosis, hyperlactacidemia (8 mmol/l), hyperammonemia (390 µmol/l) and hypoglycaemia (2.4 mmol/l). Subsequently, he developed supraventricular tachycardia, ventricular tachycardia and ultimately ventricular fibrillation resulting in cardiac arrest, which was successfully treated. A CT scan of the head revealed cerebral oedema. Whilst in the intensive care unit, he developed renal failure and rhabdomyolysis. The metabolic abnormalities seen at the time of admission normalised within 48 h with IV glucose infusion. Biological investigations, including urinary organic acids and plasma acylcarnitines, showed results compatible with MCAD deficiency. Mutation analysis revealed the patient was homozygous for the classical mutation A985G. This is one of only a few reports of severe cardiac arrhythmia in an adult due to MCAD deficiency. This condition is probably under-diagnosed in adult patients with acute neurological and/or cardiac presentations.

Keywords Arrhythmia · Coma · Hypoglycaemia · Hyperammonemia · Medium-chain acyl-CoA dehydrogenase deficiency · Adult

Introduction

Inborn errors of metabolism are rare disorders. Medium-chain acyl-CoA dehydrogenase (MCAD) is a key enzyme involved in mitochondrial fatty acid oxidation (FAO). MCAD deficiency is the most common FAO defect with a clinical prevalence of about 1/15,000 to 1/19,000 [1]. It is relatively common in some European populations and individuals descended from there [2]. Most affected individuals exhibit symptoms during the neonatal period or the first 15 months of life. The clinical presentation may include acute liver dysfunction, hypoglycaemic coma and sudden unexpected death [3]. This condition is treatable using avoidance of fasting, L-carnitine supplementation and dietary control. Application of these treatment measures has been shown to improve outcomes and prevent acute life-threatening episodes [4]. Reported clinical cases are very few compared to the theoretical number of homozygous (or composite heterozygous) individuals when the prevalence is estimated by neonatal screening [5]. This suggests that most individuals with MCAD deficiency do not present with a life-threatening, acute metabolic episode during childhood. In this report we describe an adult case of MCAD

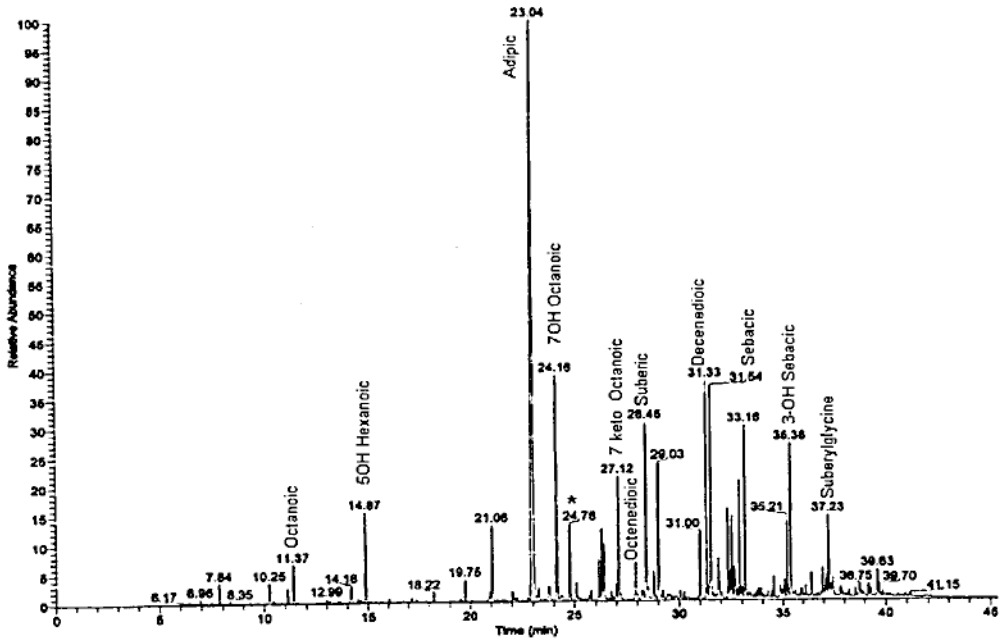

Fig. 1 The abnormal excretion of octanoic, 5-hydroxyhexanoic, adipic, 7-OH-octanoic, 7-keto-octanoic, suberic, octenedioic, sebacic, decenedioic acids and suberylglycine is strongly suggestive of MCAD deficiency

deficiency that demonstrates the critical importance of considering this disease in cases presenting with unexplained neurological or cardiac disorders and the need to collect blood and urine samples at the time of presentation to enable diagnosis.

Case report

A 33-year-old man was admitted to the Emergency Department with a 4-h history of sudden onset of lethargy, headaches and vomiting. By the time of admission he was drowsy and his speech was incoherent. He had not taken any medication. He was a heavy smoker with chronic alcoholism, but no other significant personal or familial medical history. Collateral medical history from the man's family revealed no previous episodes of metabolic decompensation during the neonatal period, childhood or adolescence. Assessment at admission showed à Glasgow coma score (GCS) of 7 (eye: 3, motor: 3, verbal: 1), blood pressure 80/60 mmHg and regular pulse at 85/min. Six hours later, he developed ventricular tachycardia, which was treated with intravenous lidocaine. After a further 8 h, he developed ventricular fibrillation with cardiac arrest, which was successfully treated by cardioversion. Atrial fibrillation occurred 2 h later and was treated using amiodarone. In the meantime, the patient's neurological status had worsened (GCS: 6), and a CT scan showed diffuse cerebral oedema. Laboratory investig ations performed on blood collected at the time of admission revealed the following abnormalities: pH: 7.49, $PaCO_2$: 16 mmHg, bicarbonates: 12 mmol/l, potassium: 5.4 mEq/l, calcium: 2.1 mmol/l, lactates: 8 mmol/l (controls <2.2 mmol/l), ammonia: 390 µmol/l (controls <50 µmol/l), glucose: 2.4 mmol/l, CK: 3,195 UI/ml (controls <220 UI/l), ASAT: 59 UI/l (controls 5–35 UI/l) and ALAT: 35 UI/l (controls 5–40 UI/l). The metabolic abnormalities gradually normalised with administration of IV glucose (175 g/day) over the ensuing 2 days. The patient remained comatose during this period. In addition to the metabolic abnormalities, this man developed acute renal failure requiring haemodialysis. The patient's clinical status subsequently improved, allowing tracheal extubation after 6 days of mechanical ventilation. Clinical recovery was complete and the patient was discharged 10 days after admission. The patient was advised to abstain from alcohol, to avoid fasting and to follow a low-fat diet with carnitine supplementation. At follow-up 1 year after discharge, he remained well and completely asymptomatic.

Extensive cardiac investigations performed during admission, including cardiac ultrasound, 24-h Holter recording, programmed electrical stimulation and coronary angiography, were normal.

In addition, detailed metabolic investigations of urine showed dicarboxylic aciduria (octanoic, 5-hydroxyhexanoic, adipic, 7-OH-octanoic, 7-keto-octanoic, suberic, octenedioic, sebacic, decenedioic acids), phenylpropionylglycine and suberylglycine (Fig. 1). The plasma acylcarnitines profile was also pathological and showed octanoylcarnitine 5.3 µmol/l (controls <0.2 µmol/l), decenoylcarnitine 1 µmol/l (controls <0.2 µmol/l) and hexanoylcarnitine 1.1 µmol/l (controls <0.4 µmol/l) (Fig. 2). Given these results, a diagnosis of MCAD was strongly suspected. The diagnosis was ultimately confirmed by molecular biology, the patient being homozygous for the common mutation A985G.

Discussion

In humans, medium-chain acyl-CoA dehydrogenase [MCAD (E.C.1.3.99.3; MIM 201450)] deficiency is the most frequently diagnosed defect of mitochondrial ß-oxidation [1]. The vast majority of patients present with metabolic crisis during the first years of life when metabolically challenged by fasting and/or viral illness. First presentation in adulthood has been described rarely [6, 7]. Usually, the phenotype includes hypoketotic hypoglycaemia, lethargy, coma, seizures and possibly death. Sudden infant death resulting from cardiac arrhythmia has also been described in relation to MCAD deficiency [8].

Numerous data can explain the cardiac toxicity of compounds that accumulate in defective fatty oxidation.

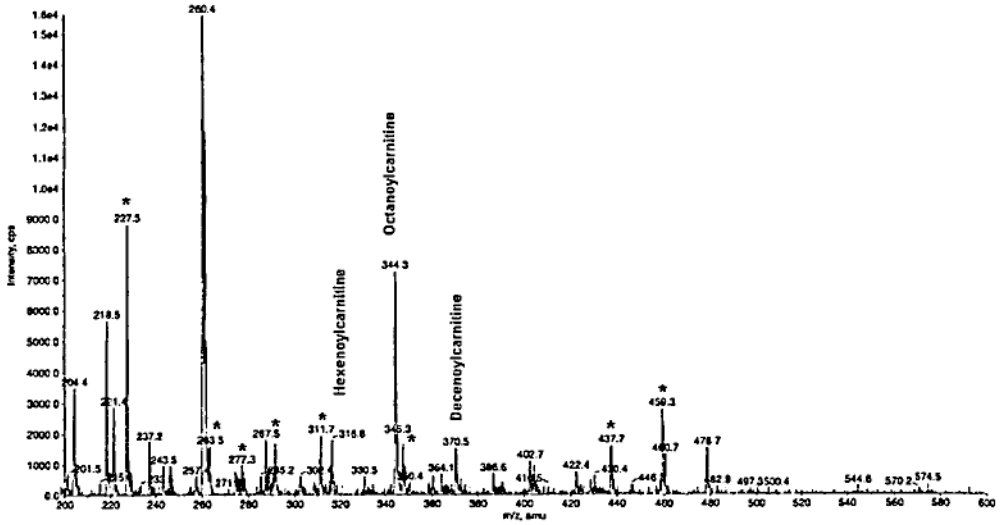

Fig. 2 The abnormal increase in hexanoylcarnitine (C_6), octanoylcarnitine (C_8) and decenoylcarnitine ($C_{10:1}$) confirms MCAD deficiency

High plasma concentrations of free fatty acids are associated with an increased incidence of ventricular arrhythmia and fibrillation in patients with acute myocardial ischemia or infarction [9]. Fatty acid oxidation is inhibited during myocardial infarction [10], leading to an accumulation of acyl-carnitine and acyl-CoA, which may lead to cytosolic calcium overload and arrhythmia [11]. The accumulation of detergent CoA derivatives and lysophospholipids also favours the development of ventricular arrhythmias.

MCAD-related coma occurs as a consequence of hyperammonemia associated with hypoketotic hypoglycaemia. In most hypoglycaemic states, ketone bodies (3-hydroxybutyrate and acetoacetate) are released from counter-regulatory lipolysis, serving as an alternative, neuroprotective fuel source for the brain [12, 13]. In MCAD deficiency, there is a reduced capacity to produce ketone bodies in response to fasting-induced hypoglycaemia. This leads to a lack of both glucose and ketone bodies as available energy sources during prolonged fasting and/or intercurrent illness. Thus, in the setting of metabolic challenge in MCAD deficiency, lactate becomes the only available energy source that can be used by the brain, and the energy that can be derived from this compound is insufficient to maintain normal brain function [14]. Moreover, ketosis increases brain uptake of neutral amino acids in exchange for glutamine. In MCAD deficiency the absence of ketone bodies could result in increased intracerebral glutamine concentrations, thus augmenting the toxic effects of concurrent hyperammonemia [15].

In our patient, MCAD deficiency was suspected given the initial findings of hypoglycaemia associated with hyperammonemia. In the urine, we found dicarboxylic aciduria and acylglycine excretion (Fig. 1), which is very suggestive of MCAD deficiency. The gold standard for diagnosis of fatty acid oxidation defects is plasma acylcarnitine profile analysis performed by tandem mass spectrometry. At admission this patient's acylcarnitine profile was typical of MCAD deficiency: increased octanoylcarnitine, decenoylcarnitine and hexanoylcarnitine (Fig. 2). Twelve h later (after glucose infusion) the profile was normal. These findings highlight the fact that in MCAD deficiency and related inborn errors of metabolism, it is crucial to perform the appropriate laboratory investigations during the acute metabolic crisis, preferably as part of the initial metabolic work-up. The typical pattern of organic acids in urine persists longer than the serum abnormalities, but is still only detectable for less than 24 h. A diagnosis of MCAD must be considered when dealing with unexplained acute digestive (vomiting), neurological (drowsiness, seizures, coma) or cardiac (arrhythmia) presentations, especially if there is an associated abnormality like hypoglycaemia, hyperammonemia, hyperlactacidemia, hepatic cytolysis or rhabdomyolysis [16].

Adult presentation of MCAD deficiency is very rare, with only two other published cases [6, 7]. Raymond [7] described the case of an unexpected death in a 45-year-old woman who fasted for 2 days in preparation for a colectomy. The diagnosis was made on postmortem analysis. The absence of past medical history, the fasting episode and the very severe presentation described in Raymond's report are very similar to our case.

This disorder is included in routine neonatal screening programs in some countries, including Germany, Australia and some parts of the U.S.A. [17, 18, 19]. These screening programs have shown that the prevalence of MCAD deficiency is much higher than estimated by clinical diagnosis. Each year in France, about six cases are clinically diagnosed, whereas the theoretical number of cases, estimated by systematic neonatal screening, is more than 40 new homozygous or composite heterozygous carriers per year [5]. These figures sug-

gest that a grseat number of adults with MCAD deficiency have never suffered symptoms. Even if they never do, this case report demonstrates that patients with this disorder can present for the first time as adults with a very severe, life-threatening, acute crisis. It is very important to reach the diagnosis, because it is a treatable disease with an excellent prognosis when given correct and timely treatment. The major goal of treatment is the prevention of metabolic decompensation by avoiding fasting (the therapeutic importance of the low-fat diet and carnitine supplementation is still under investigation). This preventive treatment either dramatically reduces or completely eliminates recurrent episodes of this disease [20].

References

1. Roe CR, Ding J (2001) Mitochondrial fatty acid oxidation disorders. In: Scriver CR, Beaudet AL, Sly W, Valle D (eds) The metabolic and molecular bases of inherited disease. McGraw-Hill, New York, pp 2297–2326
2. Tanaka K, Gregersen N, Ribes A Kim J, Kolvraa S, Winter V, Eiberg H, Martinez G, Deufel T, Leifert B, Santer R, Francois B, Pronicka E, Laszlo A, Kmoch S, Kremensky I, Kalaydjicva L, Ozalp I, Ito M (1997) A survey of the newborn populations in Belgium, Germany, Poland, Czech Republic, Hungary, Bulgaria, Spain, Turkey and Japan for the G985 variant allele with haplotype analysis at the medium-chain acyl-CoA dehydrogenase gene locus: clinical and evolutionary considerations. Pediatr Res 41:201–209
3. Boles RG, Buck EA, Blitzer MG, Platt MS, Cowan TM, Martin SK, Yoon H, Madsen JA, Reyes-Mugica M, Rinaldo P (1998) Retrospective biochemical screening of fatty acid oxidation disorders in postmortem liver of 418 cases of sudden unexpected death in the first year of life. J Pediatr 132:924–933
4. Wilson CJ, Champion MP, Collins JE, Clayton PT, Leonard JV (1999) Outcome of medium chain acyl-CoA dehydrogenase deficiency after diagnosis. Arch Dis Child 80:459–462
5. Fromenty B, Mansouri A, Bonnefont JP, Courtois F, Munnich A, Rabier D, Pessayre D (1996) Most cases of medium-chain acyl-CoA dehydrogenase deficiency escape detection in France. Hum Genet 97:367–368
6. Ruitenbeek W, Poels PJE, Turnbul DM, Garavaglia B, Chalmers RA, Taylor RW, Gabreels FJM (1995) Rhabdomyolysis and acute encephalopathy in late onset medium chain acyl-CoA dehydrogenase deficiency. J Neurol Neurosurg Psychiatry 58:209–214
7. Raymond K, Bale AE Barnes CA, Rinaldo P (1999) Medium-chain acyl-CoA dehydrogenase deficiency: sudden and unexpected death of a 45-year-old woman. Genet Med 1:293–294
8. Bennett MJ, Powell S (1994) Metabolic disease and sudden, unexpected death in infancy. Hum Pathol 25:742–746
9. Oliver MF, Kurien VA, Greenwood TW (1968) Relation between serum free fatty acids and arrhytmias and death after acute myocardial infarction. Lancet 1:710–715
10. Rosenblatt-Velin N, Montessuit C, Papageorgiou I, Terrand J, Lerch R (2001) Postinfarction heart failure in rats is associated with upregulation of GLUT-1 and down-regulation of genes of fatty acid metabolism. Cardiovasc Res 52:407–416
11. Fischbach PS, Corr PB, Yamada KA. (1992) Long-chain acylcarnitine increases intracellular Ca2+ and induces after depolarization in adult ventricular myocytes. Circulation 86:748
12. Owen OE, Morgan AP, Kemp HG, Sullivan JM, Herrera MG, Cahill GF Jr (1967) Brain metabolism during fasting. J Clin Invest 46:1589–1595
13. Robinson AM, Williamson DH (1980) Physiological roles of ketone bodies as substrates and signals in mammalian tissues. Physiol Rev 60:143–187
14. Sanchez-Abarca LI, Tabernero A, Medina JM (2001) Oligodendrocytes use lactate as a source of energy and as a precursor of lipids. Glia 36:321–329
15. Yudkoff M, Daikhin Y, Nissim I, Lazarow A, Nissim I (2001) Ketogenic diet, amino acid metabolism, and seizure control. J Neurosci Res. 66:931–940
16. Saudubray JM, Ogier de Baulny H, Charpentier C (2000) Clinical approach to inherited metabolic diseases. In: Fernandes J, Saudubray JM, van den Berghe G (eds) Inborn metabolic diseases. Diagnosis and treatment. Springer-Verlag Berlin Heidelberg New York, pp 3–41
17. Liebl B, Fingerhut R, Roschinger W, Muntau A, Knerr I, Olgemoller B, Zapf A, Roscher AA (2000) Model project for updating neonatal screening in Bavaria: concept and initial results. Gesundheitswesen 62:189
18. Carpenter K, Wiley V, Sim KG, Heath D, Wilken B (2001) Evaluation of newborn screening for medium-chain acyl-CoA dehydrogenase deficiency in 275,000 babies. Arch Dis Child (Fetal Neonatal Ed) 85:105–109
19. Ziadeh R, Hoffman EP, Finegod DN, Hoop RC, Brackett JC, Strauss AW, Naylor EW (1995) Medium-chain acyl-Coa dehydrogenase deficiency in Pennsylvania: neonatal screening shows high incidence and unexpected mutation frequencies. Pediatr Res 37:675–678
20. Iafolla AK, Thompson RJ, Roe CR (1994) Medium-chain acyl-CoA dehydrogenase deficiency: clinical course in120 affected children. J Pediatr 124:409–415