Recurrent Ventricular Tachycardia in Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

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Abstract We report a baby with medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency who presented on day 2 with poor feeding and lethargy. She was floppy with hypoglycaemia (1.8 mmol/l) and hyperammonaemia (182 μ mol/l). Despite correction of these and a continuous intravenous infusion of glucose at 4.5–6.2 mg/kg/min, she developed generalised tonic clonic seizures on day 3. She also suffered two episodes of pulseless ventricular tachycardia, from which she was resuscitated successfully. Unfortunately, she died on day 5, following a third episode of pulseless ventricular tachycardia.

Arrhythmias are generally thought to be rarer in MCAD deficiency than in disorders of long-chain fatty acid oxidation. This is, however, the sixth report of ventricular tachyarrhythmias in MCAD deficiency. Five of these involved neonates and it may be that patients with MCAD deficiency are particularly prone to ventricular arrhythmias in the newborn

period. Three of the patients (including ours) had normal blood glucose concentrations at the time of the arrhythmias and had been receiving intravenous glucose for many hours. These cases suggest that arrhythmias can be induced by medium-chain acylcarnitines or other metabolites accumulating in MCAD deficiency.

Summary Sentence Ventricular tachyarrhythmias can occur in MCAD deficiency, especially in neonates.

Abbreviations

APTT	Activated partial thromboplastin time
ECG	Electrocardiography
INR	International normalised ratio
MCAD	Medium-chain acyl-coenzyme A dehydrogenase
PCR	Polymerase chain reaction

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Introduction

Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency is an autosomal recessive disorder affecting mitochondrial fatty acid oxidation. It is one of the commonest inborn errors in populations of European descent with a reported incidence ranging from 1 in 10,000 to 1 in 27,000, based on the results of newborn screening (Grosse et al. 2006). Although the commonest age of presentation is reported to be 3 months to 3 years, both neonatal and adult cases are well described, with up to one third of patients having symptoms suggestive of MCAD deficiency in the neonatal period (Grosse et al. 2006).

Case History

Our patient was a female infant, born 13 days post-term to a primigravida mother after an uncomplicated pregnancy. The parents are unrelated Caucasians. The mother's high vaginal swab was positive for group B streptococcus, and she had one dose of antibiotics 3 h before delivery; she had history of genital herpes 9 years previously. The baby's birth weight was 3.0 kg. She was breast fed and given intramuscular vitamin K according to standard policy.

At the age of 18 h, the baby was reported to be feeding poorly but clinical examination was normal and the blood glucose was 3.7 mmol/l. At 22 h of age, she was found to be floppy, mildly jaundiced and hypoglycaemic (1.8 mmol/l). She was admitted to the neonatal intensive care and started on 10% glucose at 90 ml/kg/day (6.2 mg/kg/min). The blood glucose was 2.5 mmol/l after 1 h and subsequent values were 5.5–8.3 mmol/l. She remained on an intravenous infusion of 10% glucose continuously from this time until her death. Following a partial septic screen, she was started on intravenous penicillin, gentamicin and acyclovir.

Despite normal blood glucose concentrations, she had a left focal seizure followed by generalised clonic seizures, lasting 1–2 min, at 30 h of age. Further investigations revealed normal plasma electrolytes with a low ionised calcium (0.76–0.95 mmol/l, normal >1) and a raised urea concentration (21.9 mmol/l). Liver function tests were normal apart from a plasma bilirubin of 153 µmol/l. The plasma ammonia concentration was 182 µmol/l. A full blood count was normal but clotting screen showed mild coagulopathy with INR 2.1, prothrombin time 22.5 s (control 9.5–14.0), APTT 29.5 s (control 25–50) and fibrinogen 56 (normal 150–400 mg/dl). The calcium was corrected with intravenous calcium gluconate and the ammonia concentration returned to normal after intravenous sodium benzoate (250 mg/kg infused over 90 min). A second dose of vitamin K was given and she was treated with intravenous phenobarbital (total 40 mg/kg). The rate of the intravenous infusion was reduced because of concern about possible cerebral oedema but it continued to provide glucose at 4.5 mg/kg/min. Subsequently, the CSF culture, herpes PCR and blood culture were all negative and a cranial ultrasound was normal. She had further seizures and was treated with phenytoin (60 mg) and pyridoxine (100 mg).

The baby had two cardiac arrests on day 3, during which she was noted to have pulseless ventricular tachycardia. She was treated with cardiopulmonary resuscitation and cardioversion but sinus rhythm was only restored after intravenous boluses of normal saline, adrenaline, bicarbonate and calcium. Following the second cardiac arrest, the infant was ventilated and transferred to a tertiary neonatal unit for further management. She was hypotensive and started on a dobutamine infusion. Cerebral function monitoring was normal. ECG was unremarkable with a normal QT_c interval

but echocardiography showed impaired left and right ventricular function, patent ductus arteriosus, tricuspid regurgitation, systemic level of pulmonary artery pressure and a small patent foramen ovale. She had a further cardiac arrest on day 5, 14 h after transfer. Again, an ECG showed pulseless ventricular tachycardia but this time she died despite full resuscitation including cardioversion.

Post-mortem examination revealed a structurally normal heart with mild biventricular dilatation. The cardiomyocytes showed significant vacuolation of the cytoplasm and contained lipid on frozen sections. There was no cardiac inflammation or necrosis. The hepatic architecture was normal but there was evidence of severe diffuse microvesicular steatosis (confirmed on frozen sections). Examination of the kidney and skeletal muscles also showed lipid deposition on frozen sections. No other pathology was identified.

Methods

Fatty acid oxidation flux was measured in fibroblasts by the tritium release assay as previously reported (Olpin et al. 1999), using [9,10-³H]myristate, [9,10-³H]palmitate, [9,10-³H]oleate and [2,2,3,3-³H]octanoate.

A palmitate loading test was performed by loading cultured skin fibroblasts with [U-¹³C] palmitate and L-carnitine for 96 h, followed by quantitative acylcarnitine profiling of the incubation medium by tandem mass spectrometry essentially as previously reported (Ventura et al. 1999). MCAD activity was measured in fibroblasts using phenylpropionyl-CoA as substrate, essentially as described previously (Wanders et al. 2010).

Sequence analysis of all exons and flanking intronic sequences of the *ACADM* gene was undertaken using standard techniques. DNA from both parents was analysed by multiplex ligation-dependent probe amplification (MLPA) with probes that test for deletions spanning exons 2–4 of the *ACADM* gene (Searle et al. 2013).

Results

Blood acylcarnitine analysis showed a greatly elevated octanoylcarnitine with an increased hexanoylcarnitine and an elevated C8:C10 ratio, consistent with a diagnosis of MCAD deficiency (Table 1). Urine organic analysis was also consistent with MCAD deficiency, with increased suberylglycine and dicarboxylic acids.

Fibroblast fatty acid oxidation flux using tritiated octanoate, myristate, palmitate and oleate substrates was 12%, 35%, 54% and 65%, respectively, as compared to simultaneous controls. The pattern and degree of flux reduction were entirely consistent with MCAD deficiency.

Table 1 Plasma acylcarnitine profile

Carnitine species	Notation	Results ($\mu\text{mol/l}$)	Reference values
Free carnitine	C0	31.1	15–50
Hexanoylcarnitine	C6	1.3	<0.10
Octanoylcarnitine	C8	12.7	<0.15
Decanoylcarnitine	C10:1	0.36	<0.12
Dodecenoylcarnitine	C12:1	0.21	<0.15
Dodecanoylcarnitine	C12	0.21	<0.15
	C8:C10 Ratio	15.5	<1

A palmitate loading test revealed increased $[\text{U-}^{13}\text{C}]8$ -carnitine in the medium of the cells loaded with $[\text{U-}^{13}\text{C}]$ palmitate. These results were also consistent with MCAD deficiency.

The MCAD activity in fibroblasts was markedly reduced ($0.07 \text{ nmol}/(\text{min} \cdot \text{mg protein})$) compared to reference values (mean $\pm$ SD $0.68 \pm 0.15 \text{ nmol}/(\text{min} \cdot \text{mg protein})$), confirming MCAD deficiency.

Sequence analysis of the *ACADM* gene showed that she was heterozygous for the common c.985A>G (p.Lys329-Glu) mutation, but no second pathogenic mutation was detected. For both parents, MLPA analysis excluded deletions spanning exons 2–4 of the *ACADM* gene.

Discussions

The biochemical results leave no doubt that this baby had MCAD deficiency, though the mutation on the second allele was not identified. For all genetic disorders, there are a few patients in whom causative mutations are not identified, because they are located in parts of the gene that are not tested, such as deep intronic sequences or upstream regulatory regions.

There are now newborn screening programmes for MCAD deficiency in many countries, including North America and most of Europe. These programmes prevent a number of deaths, but, unfortunately, some MCAD deficiency patients die within a few days of birth, before the results of screening are available. Indeed, death may occur before screening samples have been obtained, particularly in the UK, where samples are obtained relatively late, between postnatal days 5 and 8. In a retrospective study, Derks and colleagues found 2 neonatal deaths among 155 Dutch patients, compared with 23 deaths after the neonatal period (Derks et al. 2006). This is, however, likely to be an underestimate of the neonatal mortality, at least for other countries. Wilcken and colleagues found 4 neonatal deaths among the 81 MCAD

deficiency patients diagnosed in Australia between 1994 and 2004 (Wilcken et al. 2007); they estimated that the risk of death subsequently during the first 6 years was 5–7% (Wilcken 2010). Most neonatal deaths due to MCAD deficiency occur by 72 h of age. Our patient presented with hypoglycaemia on day 2 and was successfully resuscitated; sadly, she went on to have further problems and died on day 5.

Deaths due to MCAD deficiency are almost invariably preceded by encephalopathy with poor feeding and increasing lethargy; it is often assumed that the final event is usually apnoea due to encephalopathy. Arrhythmias are well recognised in long-chain fatty acid oxidation defects but there have been relatively few reports in MCAD deficiency. Thus, in a series of 107 children with fatty acid oxidation disorders, 24 patients had a history of arrhythmias (Bonnet et al. 1999). These included ventricular tachyarrhythmias and supraventricular tachycardias; in 14 cases, the arrhythmia occurred in the newborn period. None of the patients with MCAD deficiency in this series, however, had arrhythmias.

It is possible that the arrhythmias in our patient were unrelated to the metabolic disorder but no other cause was identified. Moreover, there have been several recent reports of ventricular arrhythmias in patients with MCAD deficiency (Table 2). The first report concerned a 33-year-old alcoholic man who presented with vomiting, drowsiness, hypoglycaemia and hyperammonaemia (Feillet et al. 2003). He subsequently developed ventricular tachycardia, ventricular fibrillation and atrial fibrillation, which were managed with lidocaine, cardioversion and amiodarone, respectively; he also received glucose and haemodialysis. The other four cases were neonates, presenting with poor feeding and lethargy at 1–3 days of age. Two cases were hypoglycaemic and developed ventricular tachyarrhythmias from which they were successfully resuscitated (Rice et al. 2007; Sanatani et al. 2005). The third case had a metabolic acidosis but a normal blood glucose concentration (Maclean et al. 2005). Despite an intravenous infusion of

Table 2 Previous reports of arrhythmias in MCAD deficiency

References	Age	Presentation	Arrhythmia	Outcome
Feillet et al. (2003)	33 years	Vomiting, drowsiness, hypoglycaemia, hyperammonaemia	VT, VF, subsequently AF	Recovery after lidocaine, cardioversion, amiodarone, glucose, haemodialysis
Sanatani et al. (2005)	2 days	Poor feeding, lethargy, hypoglycaemia	VF	Recovery after cardioversion, glucose
Rice et al. (2007)	3 days	Poor feeding, hypoglycaemia	VT, torsades de pointes	Recovered with glucose, insulin, carnitine
Maclean et al. (2005)	3 days	Poor feeding, hypothermia pulmonary haemorrhage	Asystole, subsequently VT, VF	Recovery after glucose, cardioversion, lidocaine, amiodarone, carnitine
Yusuf et al. (2010)	30 h	Poor feeding, hypoglycaemia, apnoea	Recurrent VT, VF	Died aged 68 h despite glucose, lidocaine, cardioversion

VT ventricular tachycardia, VF ventricular fibrillation

glucose, he had a pulmonary haemorrhage associated with apnoea and an asystolic cardiac arrest. He was resuscitated and ventilated but had further cardiac arrests, associated with ventricular tachycardia and ventricular fibrillation and managed with cardioversion, lidocaine and amiodarone. The final case was particularly similar to our patient (Yusuf et al. 2010). She presented with hypoglycaemia and apnoea and was managed with ventilation and intravenous glucose. Nevertheless, she developed ventricular tachycardia and fibrillation, which responded to intravenous lidocaine. Subsequently, she was treated for hyperammonaemia and generalised seizures but ventricular tachycardia and fibrillation recurred at 65 h of age; this time the arrhythmias were resistant to antiarrhythmic drugs and cardioversion and the baby died aged 68 h.

The frequency of arrhythmias in neonates reflects the importance of fat as a fuel for the heart. This has been demonstrated by stable isotope studies in lambs (Bartelds et al. 2000) and by studying MCAD mRNA expression in rats (Kelly et al. 1989). It is interesting that arrhythmias have not been reported in older children with MCAD deficiency, although deaths most frequently occur between 6 months and 2.5 years. These deaths may result from encephalopathy and apnoea, but it is also possible that arrhythmias at this age are missed as many of the deaths occur outside hospital.

The ventricular tachyarrhythmias might potentially be induced either by increasing the automaticity of cardiomyocytes or by altering the refractory period of cardiomyocytes and allowing re-entry. The latter mechanism is favoured by the Brugada-type ECG pattern that followed the arrhythmia in one patient (Sanatani et al. 2005). Moreover, a prolonged QT_c interval has been reported in a neonate with MCAD deficiency (Wiles et al. 2014), though the QT_c interval was normal in our patient and at least one of the other patients with ventricular tachyarrhythmias (Maclean et al. 2005).

Encephalopathy and death in MCAD deficiency are often attributed to hypoglycaemia, but the accumulation of abnormal metabolites may also be responsible. Thus, there are a few reports of MCAD deficiency patients who have become encephalopathic without hypoglycaemia (Mayell et al. 2007). Our patient and that of Yusuf et al. (Yusuf et al. 2010) also had seizures at a time that their plasma glucose and ammonia concentrations were normal, several hours after brief periods of hypoglycaemia and hyperammonaemia. Cardiac arrhythmias are less likely to be directly caused by hypoglycaemia. Indeed, blood glucose concentrations were normal at the time of the arrhythmias in our patient and 2 other reports (Maclean et al. 2005; Yusuf et al. 2010). It is uncertain which metabolites contribute to the encephalopathy and cause the arrhythmias in these patients: fatty acids, acylcarnitines and acyl-CoA esters may all be responsible. Palmitoylcarnitine has been shown to affect the function of certain sodium and calcium channels in cardiomyocytes (Wu and Corr 1992; Wu and Corr 1995). Long-chain acylcarnitines at physiological concentrations (3–30 µmol/l) also affect the function of hERG potassium channels, which are involved in repolarisation (Ferro et al. 2012). These effects were not, however, observed with medium-chain acylcarnitines (Ferro et al. 2012). Fatty acids have also been shown to activate calcium channels in ventricular myocytes but, again, the effect was limited to long-chain fatty acids (Huang et al. 1992). Thus, the precise cause of the arrhythmias in MCAD deficiency remains unclear.

A sad and striking feature of our patient's history was that she continued to deteriorate with worsening ventricular tachyarrhythmias despite receiving intravenous glucose for more than 48 h. Two of the other MCAD-deficient babies were also receiving intravenous glucose (at 6.5–7 mg/kg/min) prior to their ventricular tachyarrhythmias and one had been receiving this for 35 h (Maclean et al. 2005; Yusuf et al. 2010). Most patients with MCAD deficiency

recover from acute decompensation if managed with intravenous glucose; obviously, this corrects hypoglycaemia (if present) and it is generally thought that abnormal metabolites will disappear promptly once the glucose infusion has led to a reduction in the rate of fatty acid oxidation. It is possible that the glucose infusion rates in these patients were insufficient to cause anabolism: our patient would certainly have been given more glucose if the diagnosis had been known. On the other hand, if an MCAD-deficient patient does not recover promptly with adequate intravenous glucose, it may be worth considering haemofiltration (whilst continuing the glucose infusion). Haemofiltration may have contributed to the recovery of the adult patient who presented with ventricular fibrillation (Feillet et al. 2003) as well as one with encephalopathy without hypoglycaemia (Mayell et al. 2007).

Contributions

Drs. Bala and Chetcuti looked after the patient and Dr. Bala drafted the manuscript. Dr. Morris advised on investigation of the patient and revised the manuscript. Drs. Ferdinandusse and Olpin investigated the patient and reviewed the manuscript.

Compliance with Ethics Guidelines

Conflict of Interest

Pronab Bala, Sacha Ferdinandusse, Simon Olpin, Philip Chetcuti and Andrew Morris all declare that they have no conflict of interest.

Consent

The parents of the patient reported have given written informed consent for publication.

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