Medium-chain acyl-CoA dehydrogenase deficiency

Elisabeth Jameson

John H Walter

Abstract

Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is an autosomal recessive disorder of fatty acid oxidation with an incidence in the UK of more than 1:10,000. The majority of patients are homozygous for a missense mutation c.985A > G. Newborn screening for this condition was implemented in England and Northern Ireland in 2009 in Scotland in 2010 and in Wales in 2012. Patients with MCADD are at risk during periods of fasting stress, particularly during intercurrent infections, of developing an encephalopathy associated with hypoketotic hypoglycaemia. These episodes can be prevented by giving high calorie drinks (the emergency regimen) during periods of illness but hospital admission is required for intravenous dextrose if the emergency regimen is not tolerated. No specific treatment is required at other times. This review highlights the pathogenesis, the presentation and management of MCADD.

Keywords emergency regimen; fatty acid oxidation disorder; hypoglycaemia; MCADD; medium-chain acyl-CoA dehydrogenase deficiency

MCADD review

Definition

Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is an autosomal recessive disorder of mitochondrial beta oxidation of medium chain length fatty acids. It is caused by mutations in the ACADM gene.

Epidemiology

The disorder is panethnic but more common in Caucasians with an incidence of 1 in 6000 to 10 000. 60–80% of symptomatic patients are homozygous for the c.985A > G missense mutation. A further 15–20% are compound heterozygous for c.985A > G in combination with another mutation. The prevalence of the common mutation likely reflects a founder effect and MCADD is thought to have originated in northwest Europe. The genotypes in those detected by newborn screening are more diverse suggesting that some mutations are of less clinical significance. However at present it is wise to assume that an individual with any mutation associated with persistent abnormal biochemistry (see below) is at risk from clinical illness caused by MCADD.

Elisabeth Jameson ***MBBCh BSc MRCPCH*** *is a Consultant in Paediatric Inherited Disorders of Metabolism in the Willink Biochemical Genetics Unit, Manchester Centre for Genomic Medicine, Central Manchester University Hospitals NHS Foundation Trust, Saint Mary's Hospital, Manchester, UK. Conflicts of interest: none declared.*

John H Walter ***MD FRCPCH*** *is a Consultant in Paediatric Inherited Disorders of Metabolism in the Willink Biochemical Genetics Unit, Manchester Centre for Genomic Medicine, Central Manchester University Hospitals NHS Foundation Trust, Saint Mary's Hospital, Manchester, UK. Conflicts of interest: none declared.*

Pathology

In the normal post-absorptive state there is a fall in glucose concentration with a parallel fall in insulin. This results in a release of compensatory hormones and a reduction in glucose use by muscles and peripheral tissues. Release of glucose from glycogen (glycogenolysis) initially satisfies energy demands. However, energy production from the oxidation of fats becomes increasingly important both to decrease the dependency on the limited stores of glycogen and to produce ketones that can be used as an alternative to glucose as a fuel for the brain. This is especially important in young children whose cerebral glucose requirements are high and whose physiological response to periods without enteral feeds is accelerated when compared with that in adolescents and adults. The oxidation of fatty acids is shown in Figure 1. Fatty acids released from triglycerides enter the mitochondria and subsequently undergo β-oxidation, a process by which the fatty acyl-CoA molecule is sequentially shortened by two carbon units until it is completely converted to acetyl-CoA. Electrons released from β-oxidation enter the respiratory chain to produce ATP whereas the majority of the acetyl-CoA produced is converted to ketones by the liver. Acyl-CoA dehydrogenase enzymes within this β-oxidation cycle have activities that are chain length specific: MCAD (medium-chain acyl-CoA dehydrogenase) has maximum activity for C6 to C10 fatty acids. Due to a degree of overlap in chain length specificity other β-oxidation dehydrogenases are able to oxidise medium chain fatty acids and produce ketones when flux through the pathway is low. This explains why patients with MCADD are generally able to tolerate overnight fasting. However during periods of increased requirements for β-oxidation there is an accumulation of medium-chain fatty acyl-CoA derivatives and reduced acetyl-CoA and ketone production resulting in clinical illness.

Newborn screening

Newborn screening for MCADD by tandem mass spectroscopy underwent evaluation in England between 2004 and 2006 and was implemented nationally in England and Northern Ireland in 2009 in 2011 in Scotland and in Wales in 2012. However, there are three groups of children who may still present symptomatically and in whom the diagnosis must be considered:

1. Newborns prior to the result of the newborn screening (due to inadequate breast feeding or neonatal infection), see case example below in Box 1
2. Children born prior to the newborn screening program
3. Children born in other countries where screening does not take place

Clinical presentation

The classic presentation is of encephalopathy with hypoketotic hypoglycaemia. It is important to recognise that the child may have developed an acute encephalopathy prior to the fall in blood glucose, which can lead to diagnostic confusion. It typically presents between the ages of 3 and 24 months when the child

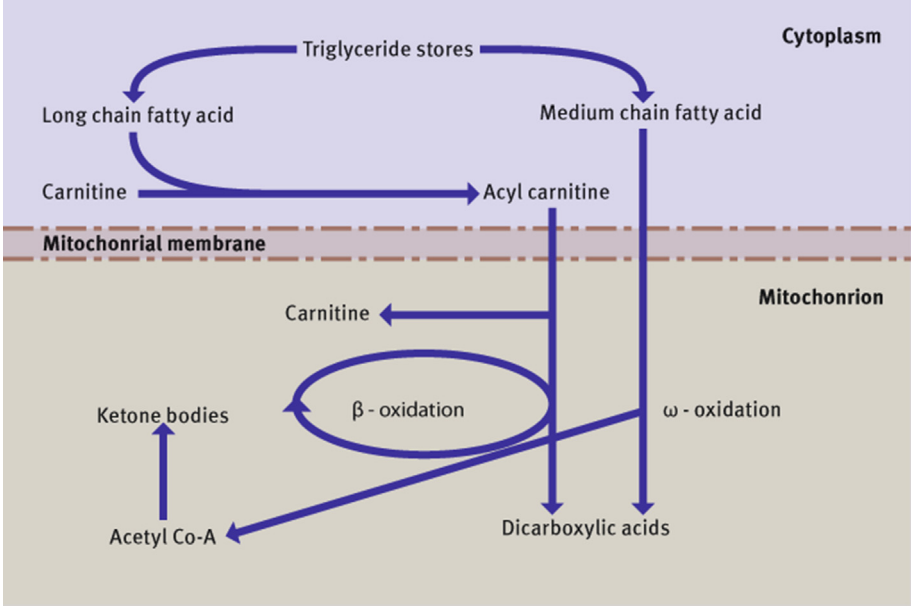

Figure 1 Fatty acid oxidation. Triglycerides are mainly composed of long chain fatty acids which require transfer across the mitochondrial membrane as an acylcarnitine. Medium chain fatty acids can cross the mitochondrial membrane directly. Within the mitochondrion fatty acids then undergo β-oxidation in which the fatty acid molecule is sequentially shortened by two carbon units releasing acetyl Co-A. Certain enzymes involved in β-oxidation, including MCAD, are chain length specific. Deficiency of this enzyme prevents the normal catabolism of both long and medium chain fatty acids and results in an increase in medium chain acylcarnitines in blood, increased ω-oxidation to form dicarboxylic acids, and a reduction in ketone body production.

Case example of early neonatal death resulting from MCADD

Baby 1 was born at term following an uneventful pregnancy. He was observed on the post-natal for 24 hours in view of prolonged rupture of membranes. He was discharged home the next day on breast feeds. On day two of life he appeared pale, though was feeding well. Later that day he became apnoeic and required resuscitation and transfer to a paediatric intensive care unit. A CT head scan was consistent with hypoxic-ischaemic encephalopathy and he remained encephalopathic. The decision to withdraw life support was made. The cause of death was thought to be sepsis, however the results of a blood spot acylcarnitine analysis showed a markedly increased C8 of 10.7 micromols/litre. Urine organic acids showed heavy dicarboxylic aciduria with traces of abnormal glycine conjugates but with no ketones. Mutation analysis went on to confirm the baby was homozygous for the common MCADD mutation c.985A > G.

The family's older children will undergo mutation analysis, even though their newborn screen was negative. Any future children will be treated as potential MCADD sufferers until tests results are back.

Box 1

experiences their first 'fast' associated with an intercurrent infection (often gastroenteritis) or being placed nil by mouth prior to a surgical procedure. The child will typically become increasingly lethargic with nausea or vomiting which rapidly progresses to coma. Hepatomegaly and hypotonia are often present. Tests done at the time will show evidence of hepatocellular dysfunction, hypoglycaemia, hypoketosis (although the presence of ketones does not exclude the diagnosis) and mild-moderate hyperammonaemia. If the low blood sugars are not detected the child may suffer a seizure, permanent neurological damage secondary to cerebral oedema and in the worst-case scenario death. In unscreened populations up to 25% of patients with MCADD have died in their first episode. Sudden unexpected death in infancy (SUDI) may be caused by undiagnosed MCADD but it is not a cause of true Sudden Infant Death Syndrome (SIDS); generally there is always a preceding illness associated with poor feeding.

Diagnosis

1. Newborn screening

Newborn screening relies on tandem mass spectrometry to detect raised C8 (octanoylcarnitine). C8 has been found to be both a specific (low number of false positives) and sensitive (low number of false negatives) marker for MCADD, particularly if combined with measurement of the C8/C10 acylcarnitine ratio. In addition to raised C8 there is also an increased urine hexanoyl glycine. Table 1 highlights the key biochemical findings in MCADD.

In the UK the newborn screening programme specifies that blood should be collected on filter paper between days 5–8 of life. Where MCADD screening is undertaken the large majority of affected infants are now detected within 2 weeks of birth. There are a number of newborns who present symptomatically prior to the newborn screening results, see Box 1.

2. Symptomatic

A child, who presents with a blood sugar less than 2.6 mmol/l, should undergo a number of investigations at the time of the hypoglycaemia (Table 2). However this may not always be achieved. Characteristic abnormalities in the urine organic acids may be transient so that samples collected when patients have recovered from an episode may not be diagnostic. Blood octanoylcarnitine, however, is always increased in MCADD.

Biochemical findings in MCADD

Investigation	Result
Blood sugar	Normal or low
Urinary or plasma ketones	Low or absent
Urine organic acids	Raised C6–C10 dicarboxylic acids (adipic, suberic and sebacic), hexonylglycine, suberylglycine and phenylpropionylglycine
Blood Acylcarnitines	Raised octanoylcarnitine (C8) and decanoylcarnitine (C10)

Table 1

Investigations to be taken at the time of hypoglycaemia

Blood	Urine
Glucose	Ketones
Acylcarnitines	Organic acids
Free fatty acids and 3(OH) butyrate	Reducing substances
Amino acids	
Ammonia	
Lactate	
Growth hormone, cortisol, thyroid function, insulin, C-peptide	

Table 2

Differential diagnosis

The differential diagnosis includes those disorders that cause encephalopathy and hypoglycaemia. Hypoketosis is associated with other inherited disorders of fatty acid oxidation and with hyperinsulinism. A significant ketosis is a feature of the majority of other causes. A careful clinical history and the investigations listed in Table 2 will usually confirm the correct diagnosis.

Management

1. **Acute illness**

It is important to emphasise that a child with MCADD may become seriously unwell before the blood sugar falls and it is imperative to treat early. All children with MCADD should have an emergency regimen for use at times of illness. The aim of the emergency regimen is to provide a source of energy and thus prevent hypoglycaemia. The emergency regimen consists of drinks usually of soluble glucose polymer (e.g. Maxijul, or Polycal) though some families use alternatives in discussion with a specialist dietician.

The principles of management of an unwell child with MCADD are given below, further detail can be found on the 'British Inherited Metabolic Disease Group' (BIMDG) website including emergency regimes; see www.bimdg.org.uk/

Stage 1. If the child is not their usual self or may be at risk of illness (for example post-immunisation) give regular oral drinks and reassess in 2–4 hours. If the child is better when re-assessed then they go back to their normal diet, if unwell then go to stage 2.

Stage 2. Regular drinks of the emergency regime to be given day and night as per the child's individual regime. This treatment should continue until the child improves. If the child does not improve go to stage 3.

Stage 3. If the child is obviously not well, not tolerating or not taking drinks or the family are worried contact or go to the hospital.

Stage 4. If the child is not tolerating or taking the emergency drinks then the child will need intravenous 10% dextrose/0.45% saline. Try to re-establish normal diet within 48 hours.

Intravenous fluids with 10% dextrose/0.45% saline must also be used if the child is nil by mouth prior to a surgical procedure.

2. **Long term management**

Throughout life the emphasis is to prevent fasting. UK recommendations for the maximum age related fasting time are given in Table 3. MCADD is not a contraindication to breast-feeding but bottle top-ups may be needed particularly in the first few days after birth. Formulas made with medium chain triglycerides are contraindicated. Weaning can be commenced at the usual time of 6 months under the guidance of a dietician. Once toddler age is reached the child needs to have three meals a day and a bedtime snack. Missed meals should be replaced with a starchy snack or sugary drink. A normal diet should be encouraged as the child grows but with inclusion of regular starchy foods. It is important that the child's school are aware of his/her disorder and are able to recognise symptoms that might be related to MCADD. Once the child reaches adolescence the issue of excess alcohol should be addressed in view of the risk of hypoglycaemia secondary to inhibition of gluconeogenesis. Individuals with MCADD are at potential risk form their disorder throughout life and should remain under review when they reach adulthood.

3. **Siblings of MCADD Patients**

Since MCADD is an autosomal recessive condition, new siblings have a 1 in 4 risk of being affected. A summary of the guidelines for their initial management after birth, provided by BIMDG, is as follows:

- Investigations should be undertaken between 24 and 48 hours of age with blood spot acylcarnitines, urine organic acids and DNA mutation analysis. Cord blood is not suitable because of the risk of maternal contamination.
- A term baby should be fed every four hours and a preterm every three hours. Potential problems associated with breast-fed babies are difficulties in quantifying the amount of breast milk taken and the low supply of breast milk in the

Recommended fasting times for children with MCADD when well

Age of child	Maximum safe fasting time (hours)
0–4 months	6
From 4 months	8
From 8 months	10
From 12 months onwards	12

Table 3

first 72 hours. These babies may need formula top-ups. If there are any concerns at all the baby should be transferred to the neonatal unit for blood sugar monitoring with appropriate management, i.e. formula feeds or intravenous 10% dextrose. These measures should continue until acylcarnitine and urine organic acid results are known.

Older siblings of patients detected by newborn screening, who were born before screening was started or born in countries without screening for MCADD should be investigated. Occasionally parents have also been found to be affected demonstrating that survival into adulthood without severe illness is possible.

Prognosis and explanation: Box 2 highlights the process following diagnosis by newborn screening and Box 3 the key points to convey to the parents. Not surprisingly parental anxiety relating to their child's management is common and families will need considerable support including direct telephone access to the specialist team.

Follow-up: children with MCADD should remain under follow-up with a specialist metabolic Paediatrician and Dietician with regular reviews in early childhood. Once middle childhood is reached, yearly reviews are usually sufficient. Parents should be allowed direct access to the local hospital's paediatric service so that lengthy waits in emergency departments (where there may be little awareness of the necessity of rapid treatment) are avoided. Copies of the emergency regimen should be provided to all relevant health professionals including the GP and local Paediatrician. Once the child reaches adolescence and is more independent as a person 'Medic-alert' bracelets are indicated.

Case example of child detected by newborn screening

Baby 2 was born at term following an uneventful pregnancy. She was a breast fed infant. She had standard blood spot testing performed on day 5 of life. This revealed a raised C8 and C10. The result was available on day 8 and immediately passed to the metabolic service. The GP was contacted that day and asked to visit the family to ensure the infant was well and to inform them that an appointment had been arranged for the baby to be seen the following day. The next day she was seen by the Consultant in inborn errors of metabolism who explained the test results and the diagnosis. Blood spots were taken for repeat acylcarnitines and also for mutation analysis. A urine specimen was collected for urinary organic acids. The result of the repeat acylcarnitine, available the same day, confirmed the diagnosis. She was then reviewed by the specialist dietician who provided guidance regarding fasting times and an emergency regime. A follow-up appointment was made for a month's time and the baby's local hospital was contacted and provided with a copy of the emergency regime should she present to them.

Box 2

Key points to convey to parents

- The outcome for a child with MCADD deficiency is excellent once the diagnosis is made. Growth, development and general health are unaffected.
- When well no special treatment is required; a normal healthy diet should be given & no specific medication is necessary.
- The recommended age related fasting times for children with MCADD when well, err on the side of caution and do not need to be shortened
- The emergency regimen must be followed during periods of illness or poor feeding to prevent complications.
- Cot death, without any preceding illness, is not caused by MCADD
- Parents should contact the specialist team if they have any concerns regarding their child.
- MCADD is a genetic disorder with a recurrence risk for further children.

Box 3

Funding

None. ◆

FURTHER READING

British Inherited Metabolic Disease Group at: http://www.bimdg.org.uk.

Clarke JTR. A clinical guide to inherited metabolic disease. Cambridge: Cambridge University Press, 2007.

UK newborn screening programme centre at: http://www.newbornbloodspot.screening.nhs.uk.

Practice points

- Children with MCADD are at significant risk of encephalopathy during periods of fasting stress, particularly associated with intercurrent infection.
- A high calorie emergency dietary regimen is given when patients are unwell to prevent clinical deterioration.
- Oral rehydration solutions do not contain sufficient glucose to prevent illness in MCADD.
- Intravenous treatment should be started immediately if the emergency regime is not tolerated.
- When children are well no treatment is required although periods without food should be limited, this depending on age (Table 3).
- Hypoglycaemia should not be relied upon as a marker of early decompensation or impending encephalopathy.