Medium-chain acyl-CoA dehydrogenase deficiency

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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.

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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:

- Newborns prior to the result of the newborn screening (due to inadequate breast-feeding or neonatal infection), see case example below in Box 1.
- Children born prior to the newborn screening programme.
- 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 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

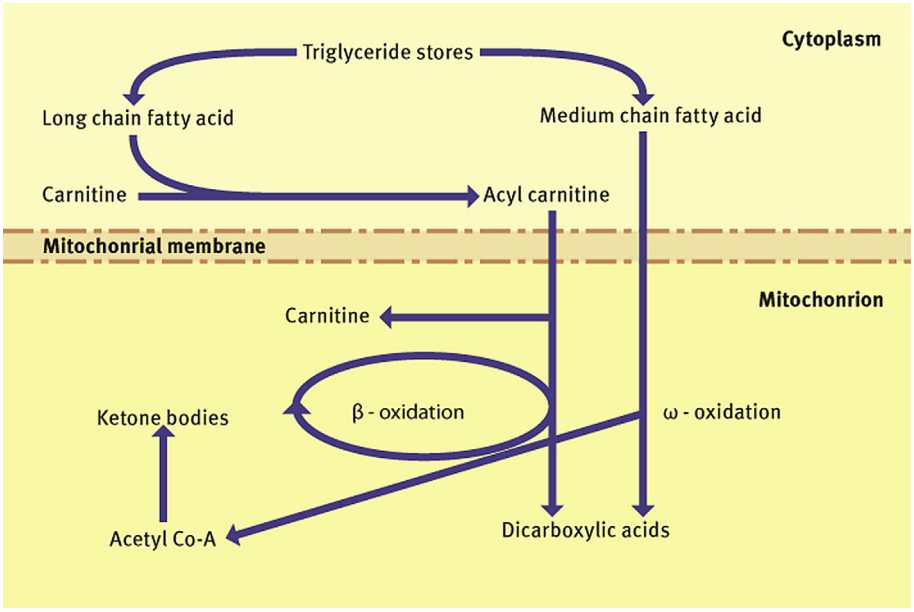

Figure 1 Fatty acid oxidation. Triglycerides are mainly composed of long chain fatty acids which require transfer across the mitochondrial membrane as an acylcarnitine. Medium chain fatty acids can cross the mitochondrial membrane directly. Within the mitochondrion fatty acids then undergo β-oxidation 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.

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.

Case example of early neonatal death resulting from MCADD

Baby one 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 μmol/L. 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

Diagnosis

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.

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