Medium-chain acyl-CoA dehydrogenase deficiency

Key facts

- Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is an autosomal recessive disorder of fatty acid oxidation that prevents the conversion of fats to energy via hepatic ketogenesis. This impairs the supply of energy to peripheral tissues, causing a continual reliance on glucose to provide energy.
- MCADD typically presents in infancy, and is precipitated by episodes of higher energy demands, for example, viral illnesses (because of the associated fever) or prolonged fasting.
- MCADD has a worldwide birth prevalence of 1 in 15,000, however this is higher in northern European populations (for example, 1 in 8,500 in the Netherlands).

Clinical features

- Patients with MCADD appear normal at birth, and usually present clinically between the age of 3 and 24 months.
- Periods of metabolic stress precipitate symptomatic episodes, which typically include poor feeding, vomiting, lethargy, drowsiness and seizures. This can quickly progress to coma and death if left untreated.
- Hepatomegaly is a common clinical sign present during an acute crisis. Biochemical abnormalities are also present, including hypoketotic hypoglycaemia, elevated liver transaminases, high ammonia and high urate.
- Some individuals remain asymptomatic until adulthood until they are given a sufficient metabolic stressor, for example, significant alcohol ingestion.

Diagnosis

- In MCADD, plasma acylcarnitine analysis has a characteristic abnormal pattern of increased C6 to C10 acylcarnitine species; C8 is usually especially elevated. This can be detected by tandem mass-spectrometry performed on dried blood spots, which is used as part of the newborn blood spot screening programme in England to diagnose MCADD. However, acylcarnitine analysis can also be performed on plasma if investigations are required in older patients.
- Urine organic acid and urine acylglycine analyses are also used in diagnosis. In MCADD, these tests demonstrate elevated C6 to C10 dicarboxylic acids, elevated hexanoylglycine and elevated suberylglycine.

Genetic basis and genetic testing

- MCADD is caused by autosomal recessive variants in the *ACADM* gene, which encodes the mitochondrial medium-chain acyl-CoA dehydrogenase (MCAD) enzyme.
- The most prevalent variant is c.985A>G, which accounts for 80% of cases.
- The carrier frequency of this pathogenic variant in Northern European populations is between 1 in 40 and 1 in 100. This high frequency means that genetic testing should be offered to reproductive partners of patients with MCADD.
- Other variants, for example, p.Tyr42His (which has an allele frequency of ~6%) are associated with some residual MCAD enzyme activity. However, individuals with this phenotype can still develop life-threatening symptoms in an acute crisis.

- Families with an affected child may benefit from genetic counselling; this is particularly important in families where consanguineous marriage is customary as there may be implications for the wider family.
- Prenatal or preimplantation genetic diagnosis requires the pathogenic variant in both parents to be identified.

Clinical management

- The most important preventative management is the avoidance of fasting. This is achieved by regular feeding in infancy, and providing older patients with complex carbohydrate before sleeping to ensure a sufficient supply of glucose overnight.
- For symptomatic patients, simple carbohydrates by mouth are the first line treatment (for example, glucose sweets).
- If patients are unable to meet their anabolic requirements orally, then IV dextrose replacement can be given. The aim of this is to maintain blood glucose levels (>5mmol/L).
- Patients have an excellent prognosis if they avoid fasting, and are managed appropriately during a crisis.
- Patients with MCADD are prone to excessive weight gain, and so should receive specialist education regarding proper nutrition and safe physical exercise.

Direction to further reading and guidelines

- Orphanet: Medium-chain acyl-CoA dehydrogenase deficiency
- Newborn blood spot screening programme: supporting publications
- Gene Review: Medium-chain acyl-CoA dehydrogenase deficiency

This information is intended for educational use and was current in November 2019. For clinical management, it is recommended that local guidelines and protocols are used.

Produced in collaboration with Imperial College Healthcare NHS Trust.