Maple syrup urine disease

Key facts

- Maple syrup urine disease (MSUD) is an autosomal recessive disorder that prevents the body from metabolising the branched-chain amino acids: leucine, isoleucine and valine.
- MSUD gets its name from the characteristic odour of affected individuals' urine.
- Approximately 1 in 116,000 infants are affected by the condition in the UK.
- The most common and severe form of the disease is the classic type that presents soon after birth. Milder variant forms also exist, and these typically present later in infancy or childhood.

Clinical features

- Classic MSUD presents soon after birth with poor feeding, vomiting and drowsiness. If left untreated, progressive encephalopathy (manifesting as intermittent apnoea and stereotyped movements, such as 'fencing' and 'bicycling'), may develop, and can ultimately lead to coma and central respiratory failure.
- Milder variant forms of MSUD present later, between the early months and early years of infancy. Affected infants may suffer from developmental delay, feeding problems and poor growth. Older children typically present with learning difficulties.
- Periods of severe catabolic stress in individuals diagnosed with MSUD can precipitate acute leucine intoxication, leading to vomiting, ataxia and altered consciousness in toddlers and hyperactivity, hallucinations and ataxia in children and adults.

Diagnosis

- Biochemical testing for the diagnosis of MSUD includes quantitative plasma amino acid and urine organic acid analysis, typically performed by specialist metabolic laboratories.
- In MSUD patients, amino acid analysis is used to detect the characteristic elevation in plasma leucine concentrations. Isoleucine and valine are typically also elevated, but may be normal or low. An elevated plasma allo-isoleucine concentration is diagnostic for MSUD.
- Organic acid analysis is used to support the diagnosis by identifying elevated branched-chain keto- and hydroxy-acids in the urine.
- MSUD may also be diagnosed by tandem mass-spectrometry analysis of leucine in dried blood spots, as part of a newborn screening programme. This analysis is part of the NHS newborn blood spot screening (NBS) programme in England.

Genetic basis and genetic testing

- MSUD is an autosomal recessive disorder caused by decreased activity of the branched-chain alpha-ketoacid dehydrogenase complex (BCKAD).
- BCKAD is comprised of four subunits (E1a, E1b, E2 and E3), and is the enzyme responsible for the second step in the catabolic pathway for the branched-chain amino acids (leucine, isoleucine and valine).
- Variants in the genes that encode three out of the four subunits of BCKAD can cause MSUD.

- In classic MSUD variants in the *BCKDHA* gene, encoding the E1a subunit, predominate. Variants in the *BCKDHB* and *DBT* genes, which encode E1b and E2 respectively, are more common in the milder variant forms.
- Affected individuals are always homozygous, or compound heterozygous for pathogenic variants in the same gene.
- Families with an affected child should be referred for 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

- Treatment of neonates with classic MSUD is a medical emergency. The goal of acute management is to promote protein anabolism and avoid catabolism by giving IV 10% dextrose/0.45% saline. In severe cases, dialysis may be required to eliminate toxic metabolites.
- The management of MSUD is centred upon avoiding the toxic accumulation of BCAAs. This is achieved by the restriction of dietary leucine and the careful manipulation of calorie intake to avoid catabolism. Patients may also be supplemented with BCAA-free amino acid formula and/or medical meals, to provide non-BCAAs and enable protein synthesis. Treatment is guided by the regular monitoring of plasma amino acid concentrations.
- MSUD patients are at risk of developing acute metabolic decompensations. This is commonly precipitated by a stressor such as infection, trauma, surgery or a significant change in diet. Patients are therefore provided with an emergency treatment protocol comprising high-calorie BCAA-free 'sick-day' formulas and aggressive dietary leucine restriction.
- Long-term dietary treatment of MSUD patients is typically managed by a specialist metabolic team including clinicians, specialist nurses and dieticians.

Direction to further reading and guidelines

- British Inherited Metabolic Disease Group: MSUD clinical management guidelines
- British Inherited Metabolic Disease Group: MSUD dietetic management pathway
- Newborn blood spot screening programme: supporting publications
- Expanded Newborn Screening MSUD Fact File

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.