Isovaleric acidaemia

Key facts

- Isovaleric acidaemia (IVA) is an autosomal recessive disorder caused by the deficiency of the enzyme isovaleryl-CoA dehydrogenase (IVD).
- IVD is responsible for the dehydrogenation of isovaleryl-CoA to produce 3-methylcrotonyl-CoA, and is involved in the metabolism of the amino acid, leucine.
- The prevalence of the condition is approximately 1 in 155,000, based on EU data.
- During episodes of acute sickness, affected individuals may exhibit a characteristic odour of sweaty feet, caused by the accumulation of isovaleric acid.

Clinical features

- The clinical severity of IVA varies from mild to life-threatening. Initially, two main phenotypes were described, an acute neonatal presentation and a chronic intermittent form, but a third phenotype now exists.
- In severe cases, symptoms typically manifest in the first few days of life. Such symptoms may include vomiting, seizures and poor feeding. If patients are left untreated, this may progress to coma and ultimately death.
- Individuals affected with the chronic intermittent phenotype may present with failure to thrive, developmental delay and learning disability.
- A third phenotype has now been described in individuals identified by newborn screening; they may be asymptomatic, and exhibit only mild elevations in IVA metabolites.

Diagnosis

- Biochemical diagnosis is achieved through the detection of elevated isovalerylcarnitine and isovalerylglycine (by acylcarnitine and urine organic acid analysis, respectively). Both compounds are typically elevated in affected patients, regardless of their metabolic condition.
- As part of the NHS newborn blood spot screening (NBS) programme in England, C5 aclycarnitine in dried blood spots is used as the initial diagnostic metabolite.
- Elevated C5 acylcarnitine may also result from increased 2-methylbutyrylcarnitine, caused by short/branched-chain acyl-CoA dehydrogenase deficiency (SBCAD) and pivaloylcarnitine, a derivative of a number of antibiotics. Further diagnostic evaluation is therefore required to confirm the diagnosis of IVA after the initial detection of raised C5 acylcarnitine by NBS.

Genetic basis and genetic testing

- IVA is an autosomal recessive condition caused by mutations in the *IVD* gene.
- The *IVD* gene encodes the enzyme isovaleryl-CoA dehydrogenase.
- A missense variant, 932C>T (A282V), has been frequently detected in patients identified by newborn screening. These patients exhibit mild elevations in isovaleryl-CoA related metabolites, and can be asymptomatic.

- Families 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 known.

Clinical management

- Treatment is managed by a multi-disciplinary team at specialised metabolic centres.
- The main goal of management is to reduce the production and increase the excretion of isovaleryl-CoA.
- Dietary treatment is focused on a low-protein, leucine-restricted diet.
- Patients may also be supplemented with carnitine and/or glycine. Carnitine and glycine are used to reduce isovaleric acid levels by the formation of the isovaleryl-CoA conjugates, which can then be excreted in the urine.

Direction to further reading and patient guidelines

- British Inherited Metabolic Disease Group: IVA Clinical Management Guidelines
- British Inherited Metabolic Disease Group: IVA Dietetic Management Pathway
- Newborn blood spot screening programme: supporting publications
- Expanded Newborn Screening IVA 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.

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