# Glutaric aciduria type I

## Key facts

- Glutaric aciduria type I (GA-I) is an autosomal recessive condition, caused by deficiency of glutaryl-CoA dehydrogenase, an enzyme involved in the catabolic pathway of lysine, hydroxylysine and tryptophan.
- GA-I has an estimated worldwide prevalence of 1 in 100,000 births, but is more frequent among certain ethnic groups (for example, the Old Order Amish community of Pennsylvania and Irish travellers).
- Undiagnosed cases typically present in the first six years of life with an acute neurological deterioration, which may be precipitated by infectious disease, vaccination or surgery. Those presenting later do so with non-specific neurological symptoms.
- Management is centred on a lysine-restricted diet and carnitine supplementation.

## Clinical features

- There is a wide spectrum of clinical severity in GA-I patients. In most cases, signs and symptoms present in infancy or early childhood, with smaller numbers presenting later in adolescence or adulthood.
- Patients may present in the neonatal period and infancy with nonspecific neurological symptoms, such as muscular hypotonia and delayed motor development.
- Macrocephaly is present at birth, or shortly after, in a large number (75%) of affected babies.
- If left untreated, most infants will suffer from an acute encephalopathic crisis, resulting in bilateral striatal injury with severe secondary dystonia, and occasionally subdural and retinal haemorrhage, which may be mistaken for the effects of child abuse.
- Patients with the late onset form may present with non-specific neurological symptoms, such as headaches, vertigo, and reduced fine motor skills, but do not develop striatal injury.

## Diagnosis

- Biochemical diagnosis involves the analysis of urine organic acids and acylcarnitines to detect the characteristic elevations in 3-OH glutaric acid, glutaric acid and glutarylcarnitine (C5DC).
- Patients may be defined biochemically as ‘high excreters’ or ‘low excreters’, based upon the degree of metabolite excretion. Although biochemically different, each group share a similar clinical course.
- Screening for GA-I is part of the NHS newborn blood spot screening (NBS) programme in England.
- C5DC acylcarnitine in dried blood spots is used as the initial diagnostic metabolite in NBS. However, this does not reliably detect low excreters that may only exhibit slightly increased C5DC levels.
- Genetic testing of the *GCDH* gene or GCDH enzyme analysis in fibroblasts/leucocytes may be used to confirm the diagnosis.

## Genetic basis and genetic testing

- GA-I is an autosomal recessive condition caused by variants in the *GCDH* gene. Over 200 variants have been reported, and DNA analysis requires sequencing of the whole gene due to the lack of a common variant.

- 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.
- Dietary treatment is focused on reduced lysine intake from a low lysine diet, and supplementation of essential amino acids with lysine-free amino acid mixtures.
- Carnitine supplementation is given in order to maintain normal plasma concentrations of free carnitine.
- Treatment monitoring requires regular quantitation of plasma amino acids levels, and should aim to maintain lysine and other essential amino acids in the normal range. Carnitine levels should also be monitored regularly.

## Direction to further reading and guidelines

- British Inherited Metabolic Disease Group: GA1 clinical management guidelines
- British Inherited Metabolic Disease Group: GA1 dietetic management pathway
- Newborn blood spot screening programme: supporting publications
- Expanded newborn screening GA1 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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