# Glutaric Aciduria Type 1

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Organic acidaemias are a class of inherited metabolic diseases characterised by the accumulation of organic acids within body tissue that are often toxic. Organic acidaemias are the consequence of an absent or defective enzyme involved in the metabolism of amino acids. Individuals with organic acidaemias are at risk of life-threatening metabolic decompensation during times of increased catabolism, for example, during illness.[1]

Glutaric aciduria type 1 (GA1) is an autosomal recessive inherited metabolic disease and is classed as an organic aciduria. The first cases were described in 1975,[2] and the literature now estimates the prevalence to be between 1 in 90,000 and 1 in 120,000 newborns worldwide.[3]

GA1 results in a deficiency in the enzyme glutaryl-CoA dehydrogenase (GCHD), which is part of the catabolic pathway in the degradation of L-lysine, L-hydroxylysine and L-tryptophan. The absence of GCHD enzyme results in an accumulation of glutaric acid (GA), 3-hydroxyglutaric acid (3-OH-GA), glutaconic acid and glutarylcarnitine (G5DC).[4, 5]

## How is GA1 diagnosed?

GA1 has been included in the panel of conditions tested via the newborn blood spot (NBS) test in the United Kingdom (UK) since 2015.[6] An NBS test is offered to all infants born in the UK, and is typically performed at day 5. Mounting evidence demonstrates that early management prior to experiencing metabolic decompensation can immensely improve the outcomes of individuals with GA1.[3]

From the dried blood spot, GA, 3-OH-GA and G5DC are detectable using tandem mass spectrometry. All patients with a positive NBS test result are referred to a Specialist Inherited Metabolic Disease Centre the same day of the result. A clinical assessment of the baby will depend on the management given at the time. Unwell babies are admitted to their local hospital for assessment, natural protein in the form of breastmilk/formula milk is stopped and an intravenous 10% dextrose infusion and carnitine is given. Natural protein is re-introduced 24-48 hours after stopping it.[7]

All patients with a positive test result are seen for further investigations, including blood, urine and genetic tests, which are used to help confirm the diagnosis of GA1.[7]

Baseline treatment involves a combination of a low lysine diet, carnitine supplementation and the provision of an emergency management plan during illness. Prior to NBS, children were commonly diagnosed after presenting with a complex movement disorder after having an intercurrent illness or after investigations due to a diagnosis of a sibling.

## Clinical outcomes of GA1

At birth infants are likely to be asymptomatic, however acute encephalopathic crisis, as a result of metabolic stress, can cause irreversible striatal injury which can subsequently result in a complex movement disorder, including dystonia.[6] Unfortunately, diet and carnitine do not reverse the symptoms of a movement disorder once it has happened. Untreated GA1 patients have a high morbidity and mortality rate, but early management has been shown to produce good outcomes.[6]

Those identified via the NBS test and who adhere to both the everyday recommended diet and medication management and, critically, when unwell follow an emergency management plan, are usually asymptomatic.[6]

## What is the treatment of GA1?

GA1 is managed by diet and medication. Carnitine supplementation is recommended lifelong and removes toxic glutaryl-CoA3 and prevents carnitine deficiency. 100 mg/kg of carnitine is started at diagnosis and the dose is doubled during illness.[3]

Alongside medication, diet is fundamental in managing GA1. Objectives of dietary management include:

- Limiting catabolism during intercurrent illness
- Ensuring a nutritionally adequate diet
- Limiting dietary intake of lysine and tryptophan
- Avoiding excessive periods of fasting
- Providing adequate energy to promote anabolism, normal growth and development.

Lysine is an essential amino acid in the diet. In GA1 the chemicals GA and 3-OH-GA can build up if too much lysine is consumed.[3] GA and 3-OH-GA are neurotoxic and, therefore, a diet low in lysine is recommended until the age of 6 years of age.[3] Limiting lysine also limits protein and this can affect overall nutritional status and growth. Given the risk of sub-optimal nutrition imposed by a protein restrictive diet, a lysine free low tryptophan mixed amino acid supplement is required.[7]

In infants, lysine can be restricted as the amount of lysine in breastmilk and standard infant formulas is known.[8] The restriction is implemented by giving a lysine free, low tryptophan specialist formula.[7] Breastfed infants are given measured amounts of lysine free, low tryptophan feed prior to being breastfed to reduce the amount of breastmilk containing lysine they consume (see **Figure 1**). Infants who are formula fed are given measured quantities of both a standard infant formula and a prescribed lysine free, low tryptophan formula (see **Figure 1**).

When infants start weaning onto food, they are introduced to the next stage of lysine free, low tryptophan amino acid supplement in preparation for them weaning off infant formula. The supplement type and amount are reviewed regularly in line with weight, age and natural protein intake.[7, 10] The supplement should continue whilst the child is on a lysine/protein restricted diet to prevent sub-optimal nutrition.

Following a lysine restricted diet is more complex when solid food is introduced. Not all foods containing protein have the same amount of lysine present. We also do not have an accurate analysis of the lysine content of all foods in the UK.[8] Individuals need more specific guidance than just following a protein restricted diet to keep plasma lysine levels within recommendations. We know that meat, fish and milk provide 70-90 mg of lysine per gram of protein and cereals and cereal-based products contain 20-40 mg lysine per gram of protein.[7, 8] To simplify, UK guidance suggests 40 mg of lysine per 1 g protein from cereal and vegetable sources and 70 mg of lysine per 1 g of protein from animal and milk protein.[7, 11] Children are given a recommendation of how much natural protein they should have daily and of this natural protein how many grams of protein should come from cereal and vegetable sources vs. animal and milk protein sources. The diet plan is guided by age/weight specific lysine dietary recommendations and plasma lysine results.

Families are taught how to read food labels and how to calculate how much of a food provides 1 g of protein. Dietary education is an important part of management. Foods naturally free from protein and therefore lysine, such as fruits and some vegetables, can be eaten freely. There are also a wide range of prescribable low protein foods, such as bread products, milk, flour, pasta, cereal, rice, meat alternatives and biscuits, to ensure children have a nutritionally balanced diet. It is useful for families to be provided with some low protein recipes to help them be able to cook nutritious meals with the prescribed products.

"When infants start weaning onto food, they are introduced to the next stage of lysine free, low tryptophan amino acid supplement in preparation for them weaning off infant formula."

**Figure 1: Adapted from BIMDG dietetic management pathway for GA1[7]**

| Dietary treatment | 0-6 months of age | 7-12 months of age |
|---|---|---|
| Lysine mg/kg/day | 114 | 114 |
| Natural protein (from breastmilk/formula/food) g/kg/day | 1.3 | 1.3 |
| Lysine free low tryptophan amino acid mix g/kg/day | 1.3-1.4 | 1 |

There is a lack of evidence recommending a low lysine diet to individuals over 6 years of age.[3] Older children can follow a less intense controlled protein diet that often involves avoiding high protein containing foods.[3]

Individuals who were not identified via newborn screening and have a movement disorder will often have feeding difficulties typically seen in individuals with neurological disease, such as swallowing difficulties. Some individuals will require a diet higher in energy due to increased energy expenditure from dystonic movements. Regular dietitian assessments are important to ensure all nutritional needs are being met.

## Dietary management during illness

Individuals with GA1 require a written illness management plan for both home and local hospital. Families should have education on how to manage illness at home and when to attend hospital, as numerous studies have demonstrated that the use of emergency management is vital in preventing neurological disorders.[6, 9, 12] Febrile illness, febrile reactions to vaccination and fasting periods during surgery can result in an acceleration of catabolism and precipitate acute encephalopathic crisis. Birth to 6 years of age is a vulnerable period for neurological insult if treatment is delayed during illness, although the emergency regimen is important even after this age.[6, 9] Emergency treatment sets out to prevent the occurrence of an encephalopathic crisis through the provision of altered nutrition during these periods.[12]

The principles of treatment include:

- Providing frequent and regular increased energy feed, consisting of a glucose polymer to provide a specific percentage of carbohydrate based on age. This can be given enterally or via intravenous fluids (IVs)[3,12]
- Preventing the risk of increased production of neurotoxins GA and 3-OG-GA by temporarily stopping natural protein for 24-48 hours[3]
- Continuing the supplementation of a lysine free, low tryptophan amino acid mix as given in maintenance therapy.[3]

If an individual is unwell at home an oral emergency regimen is started. An oral emergency regimen involves giving measured volumes of an age-appropriate glucose polymer 2-3 hourly, day and night, to prevent catabolism. The individual also needs to continue having the lysine free, low tryptophan amino acid supplement and stop all-natural protein for 24 hours.[7] If the oral emergency regimen is not tolerated at home, then prompt attendance to hospital is required.

## Nutritional & biochemical monitoring

Given the dietary restrictions it is important to monitor growth regularly. Biochemical analysis of plasma amino acids, carnitine, full blood count and nutritional bloods are also important to ensure the individual is receiving the correct carnitine supplementation and diet.[3] Individuals are monitored more frequently in the first year of life.[3] After 6 years of age the frequency of monitoring reduces as diet restriction and risk of a movement disorder reduces.[3]

## Conclusion

Dietary treatment is integral in the management of GA1, particularly from birth to 6 years of age, preventing irreversible striatal injury and the consequences. The success of implementing the diet relies upon a multidisciplinary team who specialise in inherited metabolic diseases, to provide ongoing monitoring and guidance for families.

## Learning points

- GA1 is an autosomal recessive metabolic disease and is classed as an organic acidaemia
- It is one of the conditions screened as part of the newborn screening programme, offered to all infants within the first few days of life
- GA1 results in a deficiency in the enzyme glutaryl-CoA dehydrogenase (GCHD), which is part of the catabolic pathway in the degradation of L-lysine, L-hydroxylysine and L-tryptophan. The absence of GCHD enzyme results in an accumulation of glutaric acid (GA), 3-hydroxyglutaric acid (3-OH-GA) and glutarylcaritine (G5DC)
- Dietary treatment includes following a low lysine diet with lysine free, low tryptophan and micronutrient supplements until 6 years of age
- Prompt management during intercurrent illness is essential to prevent neurological damage.

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