

# *For healthcare professionals* Glutaric aciduria type I





# Abstract

Glutaric aciduria type I (synonym, glutaric acidemia type I) is a rare organic aciduria (estimated prevalence is 1 in 100-120,000 newborns). Untreated patients characteristically develop dystonia due to striatal injury during infancy resulting in a high morbidity and mortality. Striatal injury may occur acutely during encephalopathic crises precipitated by catabolic state in infancy or develops insidiously without clinically apparent crises. Glutaric aciduria type I is caused by an autosomal recessive inherited deficiency of glutaryl-CoA dehydrogenase which gives rise to elevated (neurotoxic) glutaric acid and 3-hydroxyglutaric acid as well as (non-toxic) glutarylcarnitine in body fluids. Glutaric aciduria type I is included in the disease panel of expanded newborn screening in some countries. In the majority of patients diagnosed in the neonatal period, striatal injury can be prevented by metabolic treatment. This includes a low lysine diet, carnitine supplementation and intensified emergency treatment during acute episodes of intercurrent illness. Initiation of treatment after the onset of symptoms is generally less effective. Secondary dystonia is often difficult to treat.

## Disease name + OMIM number

Glutaric aciduria type I OMIM number: #231670

# Synonyms (if available)

Glutaricacidemia type I

Glutaryl-CoA dehydrogenase deficiency

## **Disease definition in summary**

Glutaric aciduria type I is an inherited deficiency of glutaryl-CoA dehydrogenase and is confirmed by significantly reduced enzyme activity and/or demonstration of two disease-causing mutations in the GCDH gene. The metabolic hallmark is combined elevation of glutaric acid, 3-hydroxyglutaric acid and glutarylcarnitine in urine, plasma and CSF but in a group of patients ("low excreters") metabolic screening may show (intermittently) normal results. Untreated, approximately 90% of patients, will develop a complex movement disorder with predominant dystonia due to striatal injury. This may occur acutely, precipitated by catabolism (e.g. during infectious diseases, following vaccinations or surgical interventions), or insidiously during a finite period of brain development (age 3-36 months). If the diagnosis is made during the newborn period and metabolic treatment with low lysine diet, carnitine supplementation and intermittent emergency treatment is started immediately during intercurrent illness, the irreversible striatal injury can be prevented in the majority of these patients.

## Epidemiology

Glutaric aciduria type I was first described by Goodman and co-workers in 1975. Since then more than 500 patients, with this disease, have been reported worldwide. The overall estimated prevalence is 1 in 100,000-120,000 newborns. Five populations with a high carrier frequency (up to 1:10) and overrepresentation of this disease have been identified: the Amish in Pennsylvania and the Lumbee in North Carolina, USA, the Oji-Cree first natives in Manitoba and north-western Ontario, Canada, the Irish travellers in the Republic of Ireland and Great Britain, and black South Africans.

# Etiology

The primary defect in glutaric aciduria type I is autosomal recessive inherited deficiency of glutaryl-CoA dehydrogenase (EC number 1.3.99.7), a homotetrameric, flavin adenine dinucleotide-dependent mitochondrial matrix protein that is involved in the catabolic pathways of the amino acids L-lysine, L-hydroxylysine, and L-tryptophan. The enzyme is linked to the electron transport chain



through electron transfer protein and electron transfer protein dehydrogenase. The enzyme is encoded by the *GCDH* gene which is localized on 19p13.2. The gene contains 11 exons, spans 7 kb and encodes a gene product of 438 amino acids that is imported to the mitochondrial matrix. Removal of a 44 N-terminal amino acid residue, which serves as a mitochondrial targeting sequence, from the 48.2 kD precursor peptide forms the 43.3 kD subunit of the homotetrame-ric enzyme. More than 200 (mostly private) disease-causing mutations have been described. The majority are single-base changes which are frequently localized in the hypermutable CpG sites of the *GCDH* gene. The most frequent mutation in Caucasians is c.1204C>T(p.Arg402Trp) resulting in complete loss of enzyme function. Expression studies on 4 disease-causing missense mutations showed that reduced intra-mitochondrial stability as well as impaired formation of homo- and heteromeric glutaryl-CoA dehydrogenase complexes can underlie deficient enzyme activity.

## Pathophysiology

Cerebral concentrations of glutaric acid and 3-hydroxyglutaric acid are 100-1,000 fold higher as compared to plasma. This has been demonstrated in post mortem studies in patients with a high and low excreter phenotype and in animal studies (Gcdh-deficient mice). The underlying mechanism of the steep gradient between brain tissue and blood is the very low permeability of the blood brain barrier for dicarboxylic acids including glutaric acid and 3-hydroxyglutaric acid. Although organic anion transporters (OAT) 3 (and 1) are expressed in brain capillary endothelial cells, the efflux capacity for dicarboxylic acids is low since sodium-dependent dicarboxylic acid transporters (NaDCs),which are required for functional coupling with OATs, are not co-expressed. Since L-lysine can easily enter the brain via cationic amino acid transporter (CAT) 1 and since it can be fully oxidized by neurons, glutaric acid and 3-hydroxyglutaric acid can be built in the brain but become trapped due to very limited efflux transport.

Evidence is increasing that, at high concentrations, glutaric acid, 3-hydroxyglutaric acid, and glutaryl-CoAcan act as neurotoxins. Glutaryl-CoA, which is

a structural homologue of succinyl-CoA, inhibits the 2-oxoglutarate dehydrogenase complex of the tricarboxylic acid cycle (TCA) causing impaired energy metabolism. The physiological substrate of this complex is 2-oxoglutarate which is converted to succinyl-CoA. In analogy, 2-oxoadipate is converted to glutaryl-CoA. Both succinyl-CoA and glutaryl-CoA if increasing inhibit this enzymatic complex via feedback inhibition. Glutaric acid, a 5-carbon dicarboxylic acid, inhibits the dicarboxylic acid shuttle between astrocytes and neurons. This shuttle is mediated by NaDCs. Its physiological function is transport of dicarboxylic TCA intermediates such as 2-oxoglutarate, succinate and malate from astrocytes to neurons. This is an anaplerotic mechanism which is required to compensate the constant loss of 2-oxoglutarate for the neosynthesis of the neurotransmitter L-glutamate in glutamatergic neurons. Neurons have a low pyruvate carboxylase activity and thus have limited anaplerotic capacity to compensate their losses. Therefore, the dicarboxylic acid shuttle is an important metabolic coupling between astrocytes and neurons; its interruption has significant negative consequences for energy metabolism. Cerebral energy metabolism is further impaired by disturbed regulation of cerebral blood flow in patients with glutaric aciduria type I. Intact coupling between neuronal activity, brain energy metabolism and cerebral blood flow is the cerebral key mechanism to compensate the energetic costs of increased neuronal activity. In addition, 3-hydroxylglutaric acid is thought to activate N-methyl-D-aspartate receptors thereby inducing an imbalance in excitatory and inhibitory neurotransmission and facilitating excitotoxicity.

#### **Clinical presentation**

Children with glutaric aciduria type I often show prenatal effects of the disease starting during the last trimester of pregnancy. In newborns, MR studies have identified widening of anterior temporal and sylvian CSF spaces, subependymal pseudocysts as well as signs of delayed myelination and immature gyral pattern. However, these MR abnormalities have a good prognosis and could progress or even normalize with time. Apart from occasional mild hypotonia,



irritability, and slight motor delay, the typical child with glutaric aciduria type I usually shows no neurologic abnormalities initially. Macrocephaly which initially may progress is found in 75% of patients.

Without early diagnosis and start of treatment, approximately 90% of untreated children develop acute striatal injury during a finite period of brain development (age 3-36 months). The latest reported time point of acute striatal injury is age 6 years. MR studies have demonstrated that the injury starts at the dorsolateral aspects of the putamen and progresses in a medioventral direction. Caudate and globuspallidus may also be involved. Post mortem studies revealed significant loss of striatal medium-spiny neurons. Bilateral striatal injury may occur acutely during encephalopathic crisis which may be precipitated by intercurrent febrile illness, immunization, or surgical intervention. Most symptomatic patients have suffered only a single encephalopathic crisis, whereas repetitive crises have been reported in one-third. In some patients, striatal injury may occur without preceding encephalopathic crisis. This disease variant, termed insidious onset type, has been suggested to result from perinatal injury followed by latent periods of several months before disability was apparent. Acute and insidious onset of striatal injury both characteristically result in a complex movement disorder which is best described as generalized dystonia superimposed on axial hypotonia. In infants, axial hypotonia is more prominent than in older children, and dystonia is mobile. With aging, there is a tendency towards fixed dystonia and an association with akinetic-rigid Parkinsonism. In symptomatic patients, orofacial dyskinesia is often found resulting in dysor anarthria and swallowing deficits and thus feeding problems. Children with severe dystonia often become immobile and lose previously acquired motor skills. Secondary complications such as dystrophy due to severe feeding problems, joint contractures due to immobilization, joint (sub-) luxation due to severe dystonia, and recurrent aspiration pneumonias due to swallowing deficits may develop. Symptomatic seizures may occur during encephalopathic crises although epilepsy is rare. However, patients presenting with epilepsy may be difficult to control with first- or second-line anticonvulsants. Subdural and retinal hemorrhages have been described in a few children.

A few adolescent and adult patients presented with a variable clinical symptomatology including recurrent headaches, oculomotor symptoms, gait disturbance, vertigo, reduced fine motor skills and/or hand tremor. None of them has suffered encephalopathic crisis during infancy or childhood. MR studies showed intact basal ganglia but extensive white matter abnormalities which have been mistaken as leukodystrophy. The neuropathological correlate of these changes, however, is spongy myelinopathy which is the result of intramyelinic vacuolation due to splitting of the myelin sheath along the intraperiod line. The discrepant presentation of adolescent and adult patients has suggested a late-onset disease variant. Since white matter and other extrastriatal MR abnormalities have been demonstrated also in some children (even if diagnosed and treated early) and since there is no clear-cut correlation between extrastriatal abnormalities and the clinical presentation, it remains to be elucidated whether late-onset of symptoms reflects a distinct disease variant or is the consequence of (progressive) extrastriatal changes.

The long-term outcome of the disease is yet unknown. A few adult patients have been reported. Some of them have remained asymptomatic (with or without treatment) until adulthood. The inclusion of glutaric aciduria type I to extended newborn screening programmes in some countries has identified a few mothers via transiently elevated glutarylcarnitine concentrations in dried blood spots of their newborns. The true rate of naturally occurring asymptomatic cases is unknown, however, is expected to be rare (i.e. less than 10% of patients).

#### **Diagnostic methods**

Glutaric aciduria type I can be identified by newborn screening. The diagnostically relevant metabolite is glutarylcarnitine. However, not all patients can be reliably diagnosed by this method, as there are patients with a normal or only slightly increased glutarylcarnitine concentration in dried blood spots. A few patients are known to be missed by newborn screening, particularly those with



a low excreting phenotype. The estimated sensitivity of newborn screening for glutaric aciduria type I is 95%. The differential diagnosis of positive newborn screening result includes pseudoglutarylcarnitinemia in MCAD deficiency (due to identical mass fragments of glutarylcarnitine and hydroxydecanoylcarnitine), multiple acyl-CoA dehydrogenase deficiency (glutaric aciduria type II), renal insufficiency and maternal glutaric aciduria type I.

Confirmation of positive newborn screening result or selective metabolic screening due to suspicious signs and symptoms include alternative techniques. Most commonly, analysis of glutaric acid and 3-hydroxyglutaric acid in urine (or blood) is performed using gas chromatography/mass spectrometry. Quantitative analysis of these metabolites can be achieved by stable isotope dilution assay or liquid chromatography/tandem mass spectrometry. A normal test result will make the diagnosis unlikely, but does not exclude it, in particularly not in patients with a low excreter phenotype. Alternatively, urinary concentrations of glutarylcarnitine can be analysed using tandem mass spectrometry. However, this method may also miss low excreter patients.

The only reliable confirmation of glutaric aciduria type I is the identification of two disease-causing mutations in the *GCDH* gene (~98% sensitivity) and/or the demonstration of low or lost glutaryI-CoA dehydrogenase activity (in leuko-cytes or fibroblasts), the latter still being the 'gold standard' of confirmatory diagnostic work-up.

In contrast to urea cycle defects and classical organic acidurias, glutaric aciduria type I does not cause changes in plasma amino acids or metabolic decompensation with hyperammonemia, metabolic acidosis, and elevated lactate and ketone bodies. Except for slightly and transiently elevated serum creatine kinase and alanine aminotransferase routine biochemical test results are usually normal.

## **Differential diagnosis**

The clinical and biochemical differential diagnosis for glutaric aciduria type I include dystonic cerebral palsy, secondary dystonia and basal ganglia injury due to other metabolic and infectious diseases in infancy or early childhood, conditions associated with macrocephaly, and diseases with primary or secondary evaluation of glutaric acid, 3-hydroxyglutaric acid or glutarylcarnitine. These conditions include idiopathic Leigh disease, Leigh-like diseases, propionic and methylmalonicacidurias, 3-methylglutaconic acidurias, D-2- and L-2-hydroxyglutaric acidurias, multiple acyl-CoA dehydrogenase deficiency ("glutaric aciduria type II"), and glutaric aciduria type III.

Only glutaric aciduria type II and III are associated with excretion of large amounts of glutaric acid but only patients with glutaric aciduria type II also demonstrate elevated glutarylcarnitine. However, in none of these conditions, 3-hydroxyglutarate accumulates. 3-Hydroxyglutarate but not glutarate and glutarylcarnitineis increased in ketotic patients and short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. Pseudoglutarylcarnitinemia was reported in patients with medium-chain acyl-CoA dehydrogenase (MCAD) deficiency due to interfering hydroxydecanoylcarnitine. Glutaric acid in urine and glutarylcarnitine in dried blood spots or plasma may be also elevated in patients with renal insufficiency.

In subdural and retinal hemorrhages, non-accidental head trauma needs to be considered.

#### Antenatal diagnosis and genetic counseling

Prenatal diagnosis of glutaric aciduria type I can be made by mutation analysis (if parents are carriers of disease-causing mutations), enzyme analysis in chorionic villi biopsy or cultured amniocytes or by metabolite screening in amniotic fluid (if a high excreter phenotype is expected).



## **Management and treatment**

It has been demonstrated recently that implementation of metabolic treatment and regular follow-up by specialized metabolic centres improves the outcome of patients identified by newborn screening. Therefore, metabolic treatment should be implemented by an interdisciplinary team that includes metabolic pediatricians, dietitians, and nurses. Parents and patients should have regular training and written treatment protocols.

Dietary treatment in combination with L-carnitine and emergency treatment has been demonstrated to be effective in preventing neurological disease. Recently the relative efficacy of each single component of this therapy has been evaluated, demonstrating that the neurological outcome was best in patients who received all three interventions (i.e. low lysine diet, carnitine supplementation, and emergency treatment), and that deviations from well-day treatment (i.e. low lysine diet, carnitine) resulted in an intermediate outcome. Disregard of emergency treatment recommendations, however, was associated with a poor outcome.

There is no known genotype phenotype correlation. Patients with the high and low excreter phenotype have the same risk of striatal injury if they remain untreated. This may be explained by similarly strong accumulation of glutaric and 3-hydroxyglutaric acid concentrations in the brain although urine and plasma concentrations are discrepant. Therefore, patients with the low excreter phenotype should not be mistaken as clinically "mild" disease variant. As a consequence, all patients with glutaric aciduria type I should receive metabolic treatment to prevent cerebral injury.

#### a) Basic (well-day) treatment

Low lysine diet. Dietary recommendations for natural protein, essential amino acids, energy and micronutrients (trace elements, vitamins) outlining the age-

dependent needs of a growing child are provided by international (World Health Organization) and national organisations. They are usually set to the safe level. Lysine is the quantitative most relevant precursor for the intracerebral production of glutaric acid and 3-hydroxyglutaric acid both deriving from glutaryl-CoA. To reduce lysine influx to and lysine oxidation in the brain compartment, low lysine diet aims to reduce the intake of lysine to the minimal age-dependent, individual needs, while maintaining sufficient intake of essential nutrients, minerals, micronutrients and energy substrates. To avoid malnutrition low lysine diet is often combined with the use of lysine-free, tryptophan-reduced amino acids supplements. Please note that available lysine-free products may vary in their contents; only some of them are fortified with minerals, trace elements, and vitamins.

In Gcdh-deficient mice, cerebral lysine influx and lysine oxidation could be reduced by the use of L-arginine and L-homoarginine. The underlying mechanism is competition with L-lysine at CAT1 in the blood-brain barrier and at other transporters (e.g. ORNT1 in the inner mitochondrial membrane). However, although theoretically interesting, the safety and efficacy of this concept has not yet been investigated in clinical studies.

L-Carnitine supplementation. Secondary carnitine depletion in plasma is common in untreated patients, whereas the concomitant intracellular carnitine concentrations are unknown. Conjugation of glutaryl-CoA to form non-toxic glutarylcarnitine is considered a physiological detoxification (but is quantitatively less important than in classical organic acidurias), and proposed to replenish the intracellular CoA pool. To prevent or reverse secondary carnitine depletion, andaily dosage of 100 mg carnitine per kg body weight is commonly used initially. The dosage is then adjusted to maintain plasma free carnitine concentration in the normal range.

**Riboflavin.** Riboflavin responsiveness in glutaric aciduria type I seems to be very rare. There is no standardized protocol to test riboflavin responsiveness.



Furthermore, there is no firm evidence that riboflavin improves the neurological outcome.

#### **b) Emergency treatment**

Well-day treatment alone does not prevent the manifestation of acute encephalopathic crises during catabolic state. Therefore it is crucial to start emergency treatment immediately when the patient is thought to be at risk during febrile illness, surgery and vaccinations. Emergency treatment follows the basic treatment principles of metabolic diseases of the intoxication type: (1) the prevention or reversal of a catabolic state by administration of a high-energy intake from carbohydrates (plus insulin if required); (2) reduction of neurotoxic metabolites by transient reduction or omission of natural protein for 24 (-48) hours; (3) amplification of glutarylcarnitine formation and prevention of secondary carnitine depletion by carnitine supplementation and (4) maintenance of normal hydration, electrolytes, and pH status via enteral or IV fluids.

Age-adapted and stepwise intensified protocols for emergency treatment at home and in hospital have been proposed by an international guideline group (Kölker et al. J Inherit Metab Dis 34: 677-694, 2011). After age 6 years, i.e. after the vulnerable period for acute striatal injury, emergency treatment should be considered at least during severe infectious disease. It should be performed in analogy to the protocol used for the younger age group.

#### c) Management of neurological complications

The major and most frequent complication is the manifestation of a complex movement disorder with predominant dystonia. Secondary dystonia in glutaric aciduria type I is difficult to treat, and available drugs have not been studied systematically. Dystonic patients need multi-disciplinary support. Their movement disorder should be evaluated and the therapeutic concept should be discussed by a team of experts including a neuropediatrician/neurologist, physicotherapist, occupational therapist, and other health care professionals (if required). Baclofen and benzodiazepines as monotherapy or in combination are most often used as first line treatment. Intrathecal baclofen administration has been used in success in children with severe dystonia. Anticholinergic drugs such as trihexiphenidyl should be considered as second line drug treatment for dystonia, in particular in adolescents and adults. Botulinum toxin A can be used as additional therapy for severe focal dystonia.

Stereotactic surgery (pallidotomy) for severe generalized dystonia has been reported in a few children but mostly with unsatisfactory result. Results of deep brain stimulation of globus pallidus internus or nucleus subthalamicus have not been reported in dystonic patients with this disease.

#### d) Liver and kidney transplantation

Although liver and kidneys show the highest tissue-specific activity of glutaryl-CoA dehydrogenase, liver and/or kidney transplantation will not cure the disease and should not be considered as relevantly influencing lysine oxidation in the brain. Therefore, unlike in some other intoxication type metabolic diseases (see also urea cycle defects), liver and/or kidney transplantation is <u>not</u> recommended for children with glutaric aciduria type I.

## **Prognosis**

Life expectancy of severely disabled children is significantly reduced; the 20-year-survival rate estimated from prospective studies is approximately 50%. The majority of children, in whom the diagnosis is made and treatment is started in the newborn period, have a favorable prognosis. The inclusion of glutaric aciduria type I to the screening panel of some countries and the development of evidence-based and consensus-agreed guidelines have significantly improved the neurological outcome of these children during the last decade.



# Guideline

Kölker S, Christensen E, Leonard JV, Greenberg CR, Boneh A, Burlina AB, Burlina AP, Dixon M, Duran M, García Cazorla A, Goodman SI, Koeller DM, Kyllerman M, Mühlhausen C, Müller E, Okun JG, Wilcken B, Hoffmann GF, Burgard P (2011) Diagnosis and management of glutaric aciduria type I – revised recommendations. J Inherit Metab Dis; 34: 677-694.

A German guideline ("Glutarazidurie Typ I – Diagnostik, Therapie und Management", AWMF No. 027-018, development stage S3) based on the above cited revised recommendations is available online at the website of the *Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF):* www.awmf.org/leitlinien





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For more information: http://ec.europa.eu/health/programme/policy/index\_en.htm

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