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Glutaric aciduria

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Introduction

Overview

Glutaric aciduria or acidemia type I is biochemically characterized by an accumulation of putatively neurotoxic glutaric and 3-hydroxyglutaric acid and nontoxic glutarylcarnitine. The majority of untreated individuals manifest **dystonia** due to striatal injury in infancy. Long-term observational studies, however, have demonstrated that one third of neonatally screened individuals still develop neurologic symptoms. Furthermore, progressive white matter abnormalities, subependymal nodules, malignant brain tumors, and **chronic kidney disease** have been reported in a subgroup of patients, raising concerns about the long-term disease outcome and highlighting the need for safer and more effective therapies. In this update, the author discusses the results of five studies demonstrating enlargement of the optic chiasm as a novel imaging finding. The studies showed that individuals with the high-excreter biochemical subtype have a higher risk of incidental subdural hematomas and cognitive dysfunction compared to those with the low-excreter subtype and confirmed the major impact of early diagnosis and therapeutic quality on the neurologic outcome of affected individuals.

Key points

- The precondition for preventing striatal injury is identifying patients during the newborn period when asymptomatic and starting metabolic treatment immediately.

- Intensified emergency treatment should be started without delay and before neurologic symptoms occur during each putatively threatening episode, such as infectious disease.

- Treatment should be initiated and patients should be followed by an interdisciplinary team of metabolic specialists,

dieticians, psychologists, neurologists, physical therapists, and occupational therapists.

• In a neonatally screened population, quality of therapy becomes the major predictor of neurologic outcome and survival.

Historical note and terminology

Glutaric aciduria or acidemia type I (glutaryl-CoA dehydrogenase [GCDH] deficiency) was first described in 1975 (27) and is caused by inherited deficiency of GCDH (EC 1.3.8.6), an essential enzyme for the catabolism of lysine, hydroxylysine, and tryptophan (18; 21). The human GCDH gene was assigned to chromosome 19p13.13 (29).

First observational studies included patients from the Amish community (76; 75), Saulteaux/Ojibwa (Oji-Cree) First Nations (30), and European patients (37; 36; 16; 50). The first meta-analysis evaluated published case reports of the prescreening era describing 115 post-symptomatically treated patients (05). The second meta-analysis evaluated long-term observational studies of individuals identified by neonatal screening programs (N=261) in comparison to those diagnosed after the onset of symptoms (N=386) (10). An international cross-sectional study enrolling 279 patients investigated the impact of the diagnosis and mode of therapy on the neurologic outcome and survival (46). Development of tandem mass spectrometry-based programs for expanded neonatal screening has provided the opportunity to diagnose affected individuals before onset of irreversible striatal damage (53), and to start prospective follow-up studies (76; 77; 45; 06; 33; 11).

At present, more than 700 patients have been reported worldwide. A guideline for diagnosis and management has been introduced (42) and revised twice (43; 13), and the beneficial effect of using this guideline has been confirmed (33; 11; 10; 77).

The **EIMD Patient Registry** is an international registry for intoxication type metabolic diseases and includes follow-up data for over 250 patients (48).

A variety of studies have focused on the pathogenetic mechanisms involved in acute neurodegeneration of this disease using in vitro and in vivo models and have been reviewed by various authors (47; 38; 81). Gcdh-deficient mice, an animal model for this disease, have been

developed and are still under investigation (40; 65; 64; 66; 85; 84; 20; 69).

Clinical manifestations

Presentation and course

Children with glutaric aciduria type I often show prenatal effects of the disease starting during the last trimester of pregnancy (52). Approximately 75% of affected infants have (progressive) macrocephaly (05; 46). Cranial neuroimaging demonstrates temporal cortical hypoplasia with dilated Sylvian fissures, immature gyral pattern, subependymal pseudocysts, and delayed myelination as characteristic findings in infants before irreversible striatal damage occurs (15; 32). Furthermore, the enlargement of the optic chiasm associated with signal abnormalities in the anterior intracranial visual structures are useful diagnostic clues (58). Apart from occasional mild muscular hypotonia and slight motor delay, infants with glutaric aciduria type I usually exhibit no neurologic abnormalities (45). Without early diagnosis and treatment, about 90% of untreated children develop striatal lesions (Hoffmann et 1996; 76; 46; 45; 33; 11) between three to 36 months, but no later than six years (76; 46). The major complication of striatal damage is a complex movement disorder with predominant dystonia at variable degree. With aging, the movement disorder tends to evolve from mobile to fixed dystonia and is associated with akinetic-rigid parkinsonism (26). Symptomatic seizures may occur during acute disease onset, whereas children with sudden dystonic spasms could be mistaken for epileptic seizures (17).

Opisthotonus in glutaric aciduria
This infant girl with glutaric aciduria displays axial dystonia in the form of opisthotonic posturing. (Contributed by Dr. Joseph Jankovic.)

The frequency of **epilepsy** is slightly increased in patients, and epileptic seizures may be difficult to control with first- or second-line **anticonvulsants** (56). The predominantly neurologic presentation of glutaric aciduria type I has led to the discrimination of so-called "cerebral" organic acid disorders (37) from "classical" organic acid disorders, such as methylmalonic and propionic acidurias. This terminology, however, has been challenged by the manifestation of chronic kidney disease and peripheral polyneuropathy in adult patients (35; 48; 11).

In a dystonic child with glutaric aciduria type I striatal injury becomes evident on brain MRI scans spreading in a dorsoventral direction, with the extent of the putaminal lesion predicting the severity of the movement disorder (79; 75; 32). In autopsies of deceased children, the neuropathological correlate is predominant loss of medium-spiny neurons in the neostriatum. Furthermore, spongiform myelinopathy has been demonstrated (22), and some affected children develop subdural effusions (76), which might be mistaken as **abusive head trauma** (80) and are more frequently observed in individuals with the biochemical high-excreter phenotype (12). Although the frequency of subdural hemorrhages has decreased after the implementation of **newborn screening** programs for glutaric aciduria type I, individual reports of severe acute hemorrhages after minor accidental head traumas still highlight the potential risk of this complication (83; 12).

Although acute encephalopathic crisis, precipitated by intercurrent febrile illness or another episode that triggers catabolism, was the most frequent disease manifestation in the first reported case series, it has become increasingly evident that striatal injury may also manifest insidiously and without preceding catabolic episode (16). In neonatally screened individuals, the insidious-onset form is particularly frequent in individuals who do not receive recommended dietary treatment (33; 11). In comparison to the acute-onset form, which is characterized by extensive striatal lesions and severe dystonia, the insidious-onset form is usually less severe, with putaminal lesions being restricted to the dorsolateral aspects and mild to moderate dystonia becoming clinically apparent after a latency period of a few months or even years following the detection of MRI lesions (75; 07).

Regardless of acute and insidious onset, motor dysfunction due to striatal injury is the most important and prognostically relevant complication, whereas cognitive functions have been thought to be mostly preserved (09). However, cognitive deficits may occur (02; 32; 24) and are more frequently found in the high-excreter group of patients (55).

MRI abnormalities have also been described in neonatally screened and pre-symptomatically treated patients (32). Although the striatum is spared in these individuals, MRI abnormalities are found in the pallidum, white matter, substantia nigra, nucleus dentatus, and thalamus. White matter changes and concomitant accumulation of neurotoxic metabolites and decreasing N-acetylaspartate levels are more pronounced in patients with a high excreting than a low excreting phenotype. This may have consequences for the long-term outcome (31). A few reports on high-excreting lately diagnosed adult patients with significant white matter changes and subependymal nodules on brain MRI highlight that the disease may progress into adulthood and may not be restricted to the striatum, in particular, and the central nervous system, in general (32; 35; 62). In addition, three individuals between the ages of six and 23 years presented with **medulloblastoma**,

nodular/desmoplastic variant medulloblastoma, and glioblastoma (70), respectively, raising the question of whether high-excreting individuals might be at increased risk of developing malignant brain tumors, especially if adherence to diet is poor or treatment is not started neonatally.

Although glutaric aciduria type I is considered a disease with exclusive neurologic manifestation, it has been demonstrated that some patients may also develop chronic renal failure (48; 11). Regardless of the age of diagnosis, the neurologic phenotype, and therapy, the glomerular filtration rate tends to decline with age. This first non-neurologic disease manifestation further extends the phenotypic spectrum of this disease. The mechanism remains to be elucidated. Tertiary active transport of toxic dicarboxylic acids in renal proximal tubular cells is likely to be involved. Notably, induced metabolic crisis in Gcdh-deficient mice precipitates an acute renal phenotype involving renal proximal tubules (78).

Clinical vignette

A boy of nonconsanguineous parents born at term was identified by newborn screening at seven days of age. Diagnosis was confirmed by GCDH enzyme analysis (1% residual enzyme activity), and he was found to be compound heterozygous for two pathogenic GCDH gene variants (p.Arg402Trp; p.Ala421Val). Metabolic treatment with a low-lysine diet supplemented with a lysine-free, tryptophan-reduced, and arginine-fortified amino acid mixture and carnitine supplementation was started on postnatal day eight. During the first two years of life, he was admitted to the hospital for intravenous emergency treatment once. His motor development was normal. He reached gross motor milestones in time and showed normal neuropsychological test results (Bayley Scales of Infant Development, Wechsler Preschool and Primary Scale of Intelligence). He is now five and a half years of age and has remained neurologically asymptomatic. Serial brain MRI studies were performed from the newborn period to 60 months. The initial examination revealed an immature pattern of gyration and myelination in combination with subependymal pseudocysts and wide anterior temporal and Sylvian CSF spaces. The follow-up scans documented delayed, but ultimately completed, myelination, resolution of subependymal pseudocysts, and normalization of extra-axial CSF spaces. Basal ganglia were normal the whole observation period.

Biological basis

Etiology and pathogenesis

The primary defect in glutaric aciduria type I is the deficiency of GCDH, a homotetrameric, flavin adenine dinucleotide–binding enzyme that is one of a family of mitochondrial acyl-CoA dehydrogenases linked to the electron-transport chain through electron transfer flavoprotein and electron transfer flavoprotein dehydrogenase (21). Highest tissue-specific GCDH activity is found in liver and kidney, but it is also found in neurons (84). Immunocolocalization in rats demonstrated that GCDH is widely expressed in the brain, specifically in neurons and oligodendrocytes, and in other organs (eg, liver, renal proximal tubules, intestinal mucosa, and peripheral nerves). In rat embryos, GCDH is predominantly expressed in the brain, suggesting a role for brain development (14). It remains to be elucidated whether the age- and organ-specific expression pattern correlates with the evolving clinical phenotype. GCDH is coded by the *GCDH* gene, which is located on chromosome 19p13.13 (29). More than 200 disease-causing mutations have been identified (28; 16; 86), and most patients are compound heterozygous for two different mutations. The most frequent mutation in Caucasians, p.Arg402Trp, accounts for 10% to 20% of alleles, whereas some mutations are frequently or even exclusively found in specific countries or cohorts.

GCDH is a key enzyme in the common catabolic pathway of the amino acids L-tryptophan, L-lysine, and L-hydroxylysine. It catalyzes the reaction of glutaryl-CoA to crotonyl-CoA and CO2 in two consecutive steps: dehydrogenation and decarboxylation (18).

The residual activity of the mutant GCDH varies between 3% to 30% and can be predicted by the GCDH gene variations (19). GCDH deficiency results in an insufficient flux of glutaryl-CoA to crotonyl-CoA resulting in an accumulation of upstream metabolites, especially glutaryl-CoA, which is subsequently converted to glutaric acid and 3-hydroxyglutaric acid. The formation of 3-hydroxyglutaric acid is thought to be mediated by side reactions of other mitochondrial enzymes. In the first step, glutaryl-CoA is converted at a low rate to glutaconyl-CoA by medium chain acyl-CoA dehydrogenase; the hydration of glutaconyl-CoA to 3-hydroxyglutaryl-CoA is catalyzed by 3-methylglutaconyl-CoA hydratase (60).

Postmortem examinations in patients showed that intracerebral concentrations of glutaric and 3-hydroxyglutaric acids exceed plasma concentrations by 10- to 1000-fold (22). This observation was explained by limited transport of dicarboxylic acids across the **blood-brain barrier**. Thus, glutaric and 3-hydroxyglutaric acids are trapped in the brain because these dicarboxylic acids are produced in the brain and cannot be transported across the blood-brain barrier (64) due to weak expression of organic acid transporters and lack of sodium-dependent dicarboxylic acid transporters (NaC) at the blood-brain barrier (68). It is worth noting that lysine loading, which increases the cerebral concentrations of putatively toxic glutaric and 3-hydroxyglutaric acids, has produced a clinical phenotype in young Gcdh-/--deficient mice similar to acute encephalopathic crises in infants with glutaric aciduria type I (85). Decreased susceptibility to lysine loading in adult mice was explained by a significant reduction of brain lysine influx in adult mice compared to young mice (84). Following high protein diet, IV injection of [3H]-labelled 3-hydroxyglutaric acid in these mice showed that the blood-brain barrier appears to remain intact (39).

Previous studies have provided evidence that neurodegeneration in glutaric aciduria type I might be caused by excitotoxic cell damage (47). However, this was not consistently found in all models. An alternative mechanism has been postulated. Glutaryl-CoA inhibits the 2-oxoglutarate dehydrogenase complex, a key enzyme in the tricarboxylic acid cycle (65). Lysine loading in Gcdh-deficient mice confirmed that brain injury involves impairment of cerebral energy metabolism, which was demonstrated by mitochondrial swelling and biochemical changes consistent with Krebs cycle disruption (84). It has been shown that the cerebral susceptibility to L-lysine is modulated by three factors: gender, genetic background, and lysine dosage (67). Furthermore, glutaric acid (82) and 3-hydroxyglutaric acid (72) at pathophysiologically relevant concentrations impair the transport of dicarboxylic intermediates of the tricarboxylic acid cycle, such as succinic acid, via inhibition of NaC2 and NaC3 disturbing the metabolic coupling between astrocytes and neurons (51). This mechanism, originally described to explain brain injury, is also involved in the induction of an acute renal phenotype in Gcdh-deficient mice (78).

An MR study has demonstrated that cerebrovascular changes that affect cerebral blood volume, perfusion pressure, and the autoregulatory reserve probably also contribute to this process (74). Cerebrovascular changes may result in expanded cerebrospinal fluid volume in newborns, intracranial and retinal hemorrhages in infants, and interstitial white matter edema in children and adults.

Although most studies investigated the mechanism underlying striatal injury, the mechanism of the increasingly observed extrastriatal abnormalities has remained virtually unclear. A clue to understanding might be the enhanced glutarylation of brain proteins, being exclusively localized in mitochondria of glial cells, as demonstrated in *Gcdh*-deficient mice. Glutarylation reduces the catalytic activities of

glutamate dehydrogenase and brain-specific carbonic anhydrase 5b and interferes with glutamate dehydrogenase-related protein interactions (69), changing the metabolic coupling of astrocytes and neurons. Similarly, in cultivated astrocytes, incubation with glutaric acid disturbs glutamine degradation via inhibition of glutamate dehydrogenase (49). These studies highlight that accumulation of toxic dicarboxylic metabolites is likely to chronically affect the brain metabolism of glutamate and glutamine. This mechanism may metabolically adapt glial cells to the changed metabolic demands of *GCDH*-deficient neurons (69), but in the long run to changed fluxes through Krebs cycle and the glycolytic pathway, and increased availability of glutamine may also foster tumorigenesis (70).

Epidemiology

Glutaric aciduria type I has an estimated prevalence of 1 in 125,000 newborns (11). In certain high-risk communities, up to 1 in 250 newborns is affected (30; 76).

Prevention

Prevention of the genetic disorder can be addressed through genetic counseling when carriers are identified. Prevention of neurologic injury is through careful and intensive management during the vulnerable period for encephalopathic crises. Newborn mass screening for glutaric aciduria type I by tandem mass spectrometry (53; 57) or high-risk screening of families and communities with a known increased risk can identify affected children before they suffer neurologic injury. Diagnosis and initiation of presymptomatic treatment and follow-up by a

specialized metabolic center improve the neurologic outcome (33; 11; 77). A meta-analysis comparing screened and unscreened cohorts has confirmed the major impact of newborn screening for glutaric aciduria type I on individual health, but at the same time has highlighted that therapeutic quality becomes a major predictor of neurologic outcome in screened populations (10). Extending preexisting tandem mass spectrometry-based newborn screening programs to include glutaric aciduria type I should be considered a highly cost-effective diagnostic strategy, as demonstrated by the national health systems in Germany and the United Kingdom (61; 03).

Differential diagnosis

Confusing conditions

The biochemical and clinical differential diagnosis for glutaric aciduria type I include (1) idiopathic extrapyramidal **cerebral palsy**, (2) extrapyramidal cerebral palsy secondary to other metabolic diseases, (3) organic acidurias causing neurologic disease in infancy or early childhood, and (4) other disorders causing basal ganglia injury, especially of the caudate and putamen, such as mitochondrial diseases. Principal among these conditions are idiopathic **Leigh disease**, Leigh-like diseases, propionic and methylmalonic acidurias, 3-methylglutaconic aciduria, D-2- and L-**2-hydroxyglutaric acidurias**, **multiple acyl-CoA dehydrogenase deficiency** ("glutaric aciduria type II"), and glutaric aciduria type III, which is caused by mutations in C7orf10 (71).

Only the last two disorders are associated with excretion of large amounts of glutaric acid. However, in both of these conditions, 2-hydroxyglutarate rather than 3-hydroxyglutarate accumulates. Patients with 2-oxoadipic and 2-aminoadipic aciduria have been given the diagnosis of glutaric aciduria type I because of decarboxylation of 2-oxoadipic to glutarate during processing for organic acid analysis. However, the concentration of 3-hydroxyglutarate is normal in these cases. Furthermore, 3-hydroxyglutarate excretion is increased in ketotic patients (63) and in short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. Thus, the presence of 3-hydroxyglutaric acid in

urine organic acid analysis is not pathognomonic for glutaric aciduria type I. Glutaric acid in urine and glutarylcarnitine in dried blood spots or plasma are also elevated in patients with renal failure.

Diagnostic workup

Almost all cases of glutaric aciduria type I can be identified by quantitative analysis of urinary organic acids (01). Glutaric aciduria type I can be distinguished from other causes of excessive glutaric aciduria by the presence of abnormal amounts of 3-hydroxyglutaric acid. In so-called low excreters, a subgroup of patients with a mild biochemical phenotype due to residual enzyme activity of some extent (up to 30%), glutaric aciduria type I may present as isolated 3-hydroxyglutaric aciduria (59; 16; 19). The detection of increased levels of glutarylcarnitine in dried blood spots by tandem mass spectrometry is used for newborn screening of glutaric aciduria type I (53). Some reports have demonstrated that low excreters have an increased risk for being missed by selective or neonatal screening (23; 33; 11). The diagnostic sensitivity and specificity of mass screening can be considerably increased if glutarylcarnitine is combined with glutarylcarnitine ratios (53). In any case, the diagnosis of glutaric aciduria type I should be confirmed by molecular genetic analysis and, if the analysis does not identify two known pathogenic *GCDH* gene variations, by enzyme analysis (18; 28; 86; 13).

Management

An international group of experts has developed and revised a guideline proposal for the diagnosis and management of affected patients (42; 43; 13).

Metabolic therapy. The principal therapy of glutaric aciduria type I includes (1) a low lysine diet, (2) carnitine supplementation (50 to 100 mg/kg/day), and (3) prevention or reversal of catabolic state (43; 13). When the catabolic state is more difficult to control, intravenous glucose and, if applicable, low-dose insulin infusion will rapidly suppress the amino acid and fatty acid catabolism that contribute to the intoxication. This therapeutic strategy prevents brain damage if it is started before the onset of irreversible neurologic symptoms (76; 75; 42; 33; 11) and if it promotes sufficient intake of essential nutrients and anthropometric development (08; 54).

Tube feeding. Food intake is often impaired in neurologically affected children due to difficulties in chewing and swallowing, whereas energy demand is often increased because of high muscle tone and profuse sweating. Therefore, tube feeding and careful follow-up are often necessary to guarantee a sufficient energy supply.

Arginine supplementation. Cerebral lysine influx and mitochondrial lysine import can also be modulated by arginine supplementation because lysine and arginine compete for transport across biological barriers. Accordingly, supplementation of arginine or homoarginine at high dosages show beneficial results in Gcdh-deficient (84; 66). In analogy, the use of lysine-free, arginine-fortified amino acid supplements has improved the neurologic outcome in two patient cohorts of neonatally diagnosed patients (73; 77; 41; 11).

Riboflavin. Riboflavin (100 to 200 mg/day), the cofactor of GCDH, is widely used, but its efficacy has not been proven (46), and its use is not generally recommended. Furthermore, there is no accepted definition of riboflavin responsiveness in glutaric aciduria type I.

Antidystonic treatment. Treatment of complex movement disorder with predominant dystonia remains unsatisfactory. Baclofen (orally or intrathecally), **benzodiazepines** (eg, clonazepam or diazepam), and trihexyphenidyl are recommended to treat generalized dystonia in glutaric aciduria type I, however, with variable success (13). To treat **focal dystonia**, botulinum toxin A is recommended (13).

Outcomes

The prognostically relevant event of this disease is the manifestation of striatal injury during infancy or early childhood, resulting in poor neurologic outcome and reduced life expectancy. If an infant is diagnosed at birth or before neurologic injury occurs and metabolic management is promptly initiated and follows current treatment recommendations, affected individuals with glutaric aciduria type I can have a good outcome. A growing number of observational studies and a meta-analysis have confirmed this (76; 75; 46; 45; 04; 06; 33; 34; 11; 10). Deviations from emergency treatment increase the risk of acute-onset dystonia whereas nonadherence to dietary treatment is associated with insidious-onset dystonia (33; 11). Regardless of therapy, however, kidney function tends to decline with age, starting in adolescence or adulthood (11). White matter abnormalities progress with age in individuals with the biochemical high-excreter phenotype (07).

Special considerations

Pregnancy

At present, limited information is available about pregnancies in women with glutaric aciduria type I. The effect of maternal (3-hydroxy-)glutarate levels on fetal CNS and somatic development is unknown. Three births were reported in women with glutaric aciduria type I who were previously undiagnosed and, thus, untreated (25). Two of these children showed mild neuroradiologic abnormalities at four months of age (widening of Sylvian fissures), but the abnormalities completely resolved. All children had a normal physical and neurologic development.

Anesthesia

Patients with glutaric aciduria type I have no known intolerance of specific anesthetic agents. However, they are at increased risk of CNS injury and death at the time of operative procedures because of preoperative caloric deprivation and excessive protein catabolism postoperatively. Direct management by a metabolic specialist at the time of surgery is strongly recommended, especially in young children (less than six years of age). Safe anesthetic and perioperative management have been described in single cases, including a child who underwent cardiac surgery (44).

Media

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Patient Profile

Age range of presentation

0 month to 65+ years

Sex preponderance

male=female

Heredity

heredity may be a factor

heredity typical

autosomal recessive

Population groups selectively affected

Amish

Black South Africans

Inuit Native Americans

Irish travelers

Lumbees

Occupation groups selectively affected

none selectively affected

ICD & OMIM codes

ICD-9

Glutaric aciduria: 270.7

ICD-10

Glutaric aciduria: E72.3

OMIM

Glutaric acidemia I: #231670

Questions or Comment?

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