231670

GLUTARIC ACIDEMIA I; GA1

Alternative titles; symbols

GLUTARIC ACIDURIA I
GA I
GLUTARYL-CoA DEHYDROGENASE DEFICIENCY

SNOMEDCT: 360416003, 76175005; **ICD10CM:** E72.3; **ORPHA:** 25;

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
19p13.13	Glutaricaciduria, type I	231670	Autosomal recessive	3	GCDH	608801

TEXT

A number sign (#) is used with this entry because glutaric acidemia I (GA1) is caused by homozygous or compound heterozygous mutation in the gene encoding glutaryl-CoA dehydrogenase (GCDH; 608801) on chromosome 19p13.

Description

Glutaric acidemia I is an autosomal recessive metabolic disorder characterized by gliosis and neuronal loss in the basal ganglia and a progressive movement disorder that usually begins during the first year of life (Goodman et al., 1995).

Hedlund et al. (2006) provided a detailed review of the clinical and biochemical aspects of glutaric acidemia type I.

Clinical Features

Goodman et al. (1974) described glutaric aciduria and acidemia in a brother and sister with a neurodegenerative disorder beginning at about 6 months of age and characterized by opisthotonos, dystonia, and athetoid posturing. The glutaric aciduria was increased by oral administration of L-lysine, which is metabolized through glutaryl-CoA, and was decreased by reduced protein intake. Metabolism of radioactive glutaryl-CoA was deficient in white cells, a result compatible with inherited deficiency of glutaryl-CoA dehydrogenase (Goodman et al., 1975).

Brandt et al. (1978) described a 10-year-old girl with progressive dystonic cerebral palsy. The urine contained large amounts of glutaric acid. From a review of this and 4 cases reported earlier, the authors concluded that disorders in the metabolism of organic acids should be sought in patients with progressive dystonic palsy. Lysed leukocytes from their patient showed severe impairment in the ability to metabolize glutaryl-CoA.

Amir et al. (1987) described 2 pairs of sibs with this disorder. All had a unique pattern of frontotemporal atrophy on computerized tomography (CT). Remarkably, in both sib pairs, 1 child was asymptomatic. All 12 previously reported patients had a homogeneous phenotype presenting in infancy with debilitating dystonia and choreoathetosis.

In an affected infant with glutaric aciduria, Mandel et al. (1991) described CT findings of dilatation of the insular cisterns, regression of the temporal lobes, with 'bat wings' dilatation of the Sylvian fissures and hypodensity of the lenticular nuclei. CT changes preceded the onset of symptoms by 3 months. Improvement in the temporal lobe atrophy was observed after a period of treatment, coincident with marked clinical improvement.

In 14 children with type I glutaric aciduria from the Old Order Amish community in Lancaster County, Pennsylvania, Morton et al. (1991) noted a remarkably variable clinical picture ranging from acute infantile encephalopathy and sudden death to static extrapyramidal cerebral palsy. In 10 patients, the disorder was first manifest between 3 and 18 months during an acute infectious illness. Four of these children died in early childhood, also during acute illnesses. However, there had been little progression of the neurologic disorder after age 5 years in the surviving children, and intellect was usually preserved even in children with severe spastic paralysis. They suggested that restriction of dietary protein and limitation of protein catabolism, dehydration, and acidosis during illnesses may prevent the onset or progression of neurologic disease in Amish patients with this disorder. Morton et al. (1991) presented a pedigree chart tracing both parents of all except one case to John Lapp and his wife, who immigrated to the United States in the 1730s. The oldest patient was a 28-year-old man who was normal until age 3 months when, after a period of irritability and poor feeding on day 7 of a varicella infection, he experienced an acute, afebrile episode of tonic posturing and thereafter became flaccid and unresponsive. After recovery from the acute episode, which was diagnosed as varicella encephalitis, he was left

with a residual spastic diplegia, partial bulbar palsy, and choreoathetosis. GA I was diagnosed based on a urinary glutaric acid level of 166 mg/g creatinine. Despite spastic diplegia and moderate choreoathetosis, he had normal intelligence and regularly worked in a carriage and harness repair shop. There had been no apparent progression of his neurologic disease since the single damaging illness at age 3 months.

Kyllerman et al. (1994) reported 12 new cases, aged 9 months to 16 years, comprising all known cases of GA I in Sweden and Norway. Ten had a severe dystonic-dyskinetic disorder, 1 had a mild hyperkinetic disorder, and 1 was asymptomatic. Two children died in a state of hyperthermia. Carnitine deficiency and malnutrition developed in patients with severe dystonia and dysphagia, which necessitated replacement therapy and gastrostomy. A slowly progressive dyskinetic disorder developed in 1 subject despite adequate early dietary treatment. Macrocephaly was found in 3. Computed tomography and magnetic resonance investigations in 10 showed deep bitemporal spaces in 7. Neuropsychologic testing of 8 of 12 subjects demonstrated receptive language function to be superior to expressive language and motor function, although cognitive functions were less affected than motor functions. A review of 57 pooled cases demonstrated that a severe dystonic syndrome developed in 77% and a mild extrapyramidal syndrome in 10%, while 12% were asymptomatic.

Hoffmann et al. (1995) presented the clinical findings in more than 21 patients with GCDH deficiency. Seventy-six percent of the patients presented with an acute encephalopathic crisis, mostly associated with an upper respiratory and/or gastrointestinal infection between the ages of 2 and 37 months. The metabolic symptoms, such as hypoglycemia and metabolic acidosis, were minimal. After recovery the children had lost most motor skills and functioned at a 1- to 2-month-old level. At that point, the very distinctive clinical picture of a severe dystonic-dyskinetic syndrome in alert-looking children with relatively well-preserved intellectual functions and a prominent forehead could be recognized. About one-fourth of the patients never suffered encephalopathic crisis but presented with subacute motor delay. These patients showed developmental delay from birth and a progressive dystonic 'cerebral palsy.' Hoffmann et al. (1995) observed that, whereas in most patients with GCDH deficiency there is often remarkable discrepancy between the severe motor impairment and the normal or near-normal intellectual functions until late in the disease process, children who never develop normally are more likely to be impaired mentally. Forty-three percent of this series showed macrocephaly at birth and 67% showed macrocephaly in infancy. Profuse sweating was noted in 35%.

Merinero et al. (1995) described 7 new patients with severe deficiency of glutaryl-CoA dehydrogenase in cultured skin fibroblasts, only 3 of which excreted high levels of glutaric acid in the urine. High levels of glutaric acid were seen in the spinal fluid of all these patients. The patients presented between 6 months and 2 years of age with either seizures or hypotonia and dystonia. All but 1 had severe impairment of psychomotor development and abnormalities on T2-weighted MRI, chiefly bilateral hyperdensities of basal ganglia, atrophy of the temporal lobe, or extensive white matter hypodensities.

Bjugstad et al. (2000) performed a forward, stepwise, multiple regression analysis to find predictors for outcome in 115 previously described patients with glutaric acidemia type I. The analyses showed that in patients who did not have a precipitating illness before the first appearance of motor symptoms, the age at onset was significantly associated with the severity of motor impairments and overall clinical outcome. In patients who had a precipitating illness, the age at onset did not predict the outcome. In both groups of patients, basal ganglia degeneration, enlargement of spaces containing cerebrospinal fluid, and white matter abnormalities were indicative of a poorer prognosis. Treatment given after the appearance of symptoms was not associated with a better clinical outcome or fewer motor deficits.

In a discussion of the natural history of GA I, Strauss et al. (2003) commented that micrencephalic macrocephaly is a distinctive radiologic feature of GA I. In most neonates, an enlarged head circumference is the only presenting sign of the disorder. The authors pointed to radiologic signs of large fluid collections in the middle cranial fossae. Veins could be seen stretching tenuously across this space, where they are subject to distortion and rupture. Acute subdural hemorrhage can occur after minor head trauma and in some instances is accompanied by retinal hemorrhages. Investigation of child abuse preceded a correct metabolic diagnosis in some non-Amish children.

Strauss et al. (2003) summarized the clinical characteristics of 37 Amish and 40 non-Amish patients with GA I. Of the Amish patients, 17 were identified retrospectively and 20 were treated prospectively following diagnosis through screening of asymptomatic newborns. In all groups, basal ganglia degeneration was the major determinant of functional disability. The incidence of basal ganglia injury was 85% in non-Amish patients and 94% in retrospectively identified Amish children. In the other 20 Amish children, most of them diagnosed by neonatal screening, prospective management was accompanied by a basal ganglia injury rate of 35%. Acute striatal necrosis was the major cause of morbidity and mortality, and dystonia caused chronic medical and surgical complications. In older patients, exercise intolerance, hypoglycemia, and seizures often developed. Strauss et al. (2003) stated that fasting hypoglycemia probably has 2 distinct causes in GA I: nonketosis and hypoketosis. The former results from carnitine deficiency, which can also give rise to myopathy, cardiomyopathy, and Reye-like hepatocerebral crisis, and the latter can occur during intercurrent illness even in carnitine-supplemented children.

Bahr et al. (2002) reported a previously healthy 19-year-old woman who presented with recurrent headaches, oculomotor symptoms, and a severe leukoencephalopathy on MRI. Subsequent evaluation revealed increased urinary glutaric acid and compound heterozygosity for mutations in the GCDH gene.

Kulkens et al. (2005) reported 2 unrelated patients who developed neurologic signs at ages 35 and 15 years, respectively. The first patient had onset of headaches at age 35, developed tremor of both arms at age 50, and had 6 tonic-clonic seizures between ages 54 and 62. At age 63, he developed ataxia, progressive dementia, and speech problems. The other patient developed headache, vertigo, and gait disturbance at age 15 years following an upper respiratory tract infection. Both patients had macrocephaly from birth and showed supratentorial leukoencephalopathy. Genetic analysis confirmed glutaryl-CoA dehydrogenase deficiency. Clinical treatment resulted in improvement and full recovery, respectively.

Despite early diagnosis, one-third of Amish infants with glutaryl-CoA dehydrogenase deficiency developed striatal lesions that leave them permanently disabled. To better understand mechanisms of striatal degeneration, Strauss et al. (2007) retrospectively studied imaging results from 25 Amish patients homozygous for the 1296C-T mutation in GCDH (608801.0002). Asymptomatic infants had reduced glucose tracer uptake and increased blood volume throughout the gray matter, which may signify predisposition to brain injury. Striatal lesions developed in 9 children (36%): 3 had sudden motor regression during infancy, whereas 6 had insidious motor delay associated with striatal lesions of undetermined onset. Acute striatal necrosis consisted of 3 stages: (1) an acute stage within 24 hours of motor regression, characterized by

cytotoxic edema within the basal ganglia, cerebral oligemia, and rapid transit of blood throughout the gray matter; (2) a subacute stage, 4 to 5 days after the onset of clinical symptoms, characterized by reduced striatal perfusion and glucose uptake, and supervening vasogenic edema; and (3) a chronic stage of striatal atrophy. Strauss et al. (2007) suggested that intravenous fluid and dextrose therapy for illnesses during the first 2 years of life was the only intervention that was clearly neuroprotective in these patients.

Marti-Masso et al. (2012) reported 2 adult Spanish sisters with onset in infancy of a severe progressive form of dystonia affecting the upper and lower limbs, face, neck, and trunk, and resulting in severe speech impairment and the inability to walk by the teenage years. Neither had macrocephaly, organomegaly, cognitive impairment, or acute encephalopathy in childhood. Whole-exome sequence analysis identified a homozygous mutation in the GCDH gene (V400M; 608801.0008), consistent with glutaric acidemia. Laboratory studies showed decreased long-chain acylcarnitines and high excretion of 3-hydroxyglutaric acid, but urinary glutaric acid excretion was normal. Brain imaging showed increased signals in the lenticular nuclei. The findings implicated mitochondrial fatty acid metabolism as an important pathway in the development of dystonia, and Marti-Masso et al. (2012) concluded that GCDH mutation analysis should be considered in the differential diagnosis of progressive forms of early-onset generalized dystonia.

Clinical Management

Heringer et al. (2010) summarized the guidelines published by Kolker et al. (2007) for the management of glutaryl-CoA dehydrogenase deficiency. Recommendations included a lysine-restricted diet to reduce the accumulation of the neurotoxic metabolites glutaric acid, 3-hydroxyglutaric acid, and glutaryl-CoA deriving from the precursor amino acid lysine; the supplementation of carnitine to prevent secondary carnitine depletion, to facilitate production of the nontoxic C5DC, and to replenish the intracellular free coenzyme A pool; and the intermittent and stepwise intensification of metabolic treatment using a high-calorie, low- or no-protein emergency treatment protocol during putatively threatening episodes such as infectious disease to prevent striatal injury. Heringer et al. (2010) assessed the outcome of 52 patients identified by a newborn screen in Germany from 1999 to 2009. Outcome was evaluated in relationship to therapy and therapy-independent parameters. According to following the guidelines of Kolker et al. (2007), Heringer et al. (2010) found that outcome was best in glutaric aciduria-1 patients who were treated in full accordance with treatment recommendations (n = 37; 5% had movement disorder (MD)). Deviations from recommended basic metabolic treatment (low-lysine diet, carnitine) resulted in an intermediate outcome (n = 9; 44% MD), whereas disregard of emergency treatment recommendations was associated with a poor outcome (n = 6; 100% MD). Treatment regimens deviating from recommendations significantly increased the risk for movement disorder (OR, 35; 95% CI, 5.88-208.39) and acute encephalopathic crises (OR, 51.32; 95% CI, 2.65-993.49). Supervision by a metabolic center improved the outcome (18% vs 57% MD; OR, 6.17; 95% CI, 1.15-33.11), whereas migrational background and biochemical phenotype (high vs low excretor status) had no significant effect.

Diagnosis

Kyllerman et al. (1994) noted that glutaric aciduria may go undetected in patients with cerebral palsy and mental retardation. In patients suspected of having the disorder, repeated examinations of organic acids in the urine and enzyme assay may be necessary to confirm the diagnosis.

Tortorelli et al. (2005) found that the urinary excretion of glutarylcarnitine is an informative tool in the biochemical diagnosis of glutaric acidemia I in patients with inconclusive biochemical findings.

Prenatal Diagnosis

Goodman et al. (1980) monitored 2 pregnancies at risk for glutaric acidemia type I. In 1 case in which the fetus was unaffected, glutaric acid was not detected in the amniotic fluid at amniocentesis (15 weeks) and the glutaryl-CoA dehydrogenase activity of cultured amniotic cells was normal. In the other case, there was a marked increase of glutaric acid in the amniotic fluid as well as a deficiency of glutaryl-CoA dehydrogenase in cultured amniotic cells. The pregnancy was terminated, and postmortem studies confirmed the diagnosis of glutaric acidemia.

Christensen (1994) described experience with chorionic villus sampling for first-trimester diagnosis of this disorder. Among 16 pregnancies, 4 were predicted to represent an affected fetus; in 3 of the affected cases, GCDH activity was measured in both uncultured and cultured chorionic cells and the correct diagnosis was established by both measurements.

Molecular Genetics

In a Navajo child with glutaric acidemia type I, Biery and Goodman (1992) and Goodman et al. (1995) identified homozygosity for a mutation in the GCDH gene (608801.0001).

Among 64 unrelated patients with glutaric acidemia type I, Biery et al. (1996) identified 12 mutations and several polymorphisms in 7 exons of the GCDH gene (see, e.g., 608801.0007-608801.0009). Several mutations were found in more than one patient, but no one prevalent mutation was detected in the general population. However, a single mutation was found as the cause of glutaric acidemia in the Old Order Amish of Lancaster County, Pennsylvania (A421V; 608801.0002).

Population Genetics

Morton et al. (1989, 1991) described type I glutaric aciduria in 14 children from the Old Order Amish community in Lancaster County, Pennsylvania. The authors estimated a 10% carrier frequency for this disorder among the Lancaster County Old Order Amish.

Among 48 individuals with confirmed GCDH deficiency, Zschocke et al. (2000) identified a total of 38 different mutations. R402W (608801.0004) was the most common mutation in Europeans, accounting for 40% of alleles in patients of German origin.

Glutaric acidemia type I occurs in about 1 in 100,000 infants worldwide (Hedlund et al., 2006).

See Also:

Bennett et al. (1986); Leibel et al. (1980); Stutchfield et al. (1985)

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