

Disease Name:

GLUTARIC ACIDURIA TYPE I

(GA I; GLUTARIC ACIDURIA I; GLUTARYL-CoA DEHYDROGENASE DEFICIENCY)

Classification:

Organic Aciduria

Genetic Information:

Inheritance: Autosomal recessive

Population Incidence: 1:40,000 in Caucasians and 1:30,000 in Sweden

Ethnic Incidence: 1/10 carrier frequency among certain inbred populations, particularly the Old Order Amish in Pennsylvania and the Ojibway Indians in Canada.

Gene & Location: GCDH; 19p13.2

Common Mutation: No common mutation, with the exception of the above-mentioned populations.

OMIM # *231670

Disease Information:

Symptom Onset: Infancy, typically 2-37 months

Symptoms: 70% of patients have macrocephaly at or shortly after birth. There may be soft neurologic signs like jitteriness, irritability and truncal hypotonia in the newborn period. There are several different clinical presentations: 1). Affected infants appear normal and then suffer an acute metabolic crisis, usually 6-18 months, with subsequent neurological findings that improve slightly then remain static. . Changes in the basal ganglia in particular, atrophy of the caudate and putamen develop within a few days or weeks of encephalopathic episode. Neuronal loss and fibrous gliosis occur in the caudate and putamen as part of neurotoxicity of GA I. 2). Infants have a period of normal development, acute crisis and subsequent neurological findings similar to those above, but then progress slowly with recurrent episodes of ketosis, vomiting, hepatomegaly and encephalopathy when the child develops infections.3). Approximately 25% of infants gradually develop motor delay, hypotonia, dystonia and dyskinesia during the first few years of life without any apparent acute crisis. 4). Individuals can be completely asymptomatic without any crises and normal development. This has been documented via carrier testing and identification of 5% of affected Amish without symptoms. Some of these adults have now been diagnosed with white matter changes.

Physical Findings: Macrocephaly, cerebral palsy, dystonia.

Treatment: Prompt treatment of catabolic events with fever control, IVF, glucose, insulin and carnitine may prevent neurologic symptoms in patients without striatal damage at diagnosis. The effect of treatment with riboflavin and diet restriction of lysine and tryptophan is less clear. Hospital admission is mandatory for IV fluids with any vomiting illness. Patients appear to do better if started on high-dose IV carnitine during illnesses.

Natural History without treatment: Most symptomatic patients, if untreated, die within the first decade of life. Patients may have recurrent fevers not related to illness. There are reports of 2 children dying from hyperthermia, so fever control is essential. Patients may also have profuse sweating, either central or peripheral in origin.

Natural History with treatment: Presymptomatic diagnosis has proven to have a better outcome than identifying patients after their first encephalopathic event. Even with prospective treatment 35% of patients will have neurological insult and disability.

Metabolic Information:

Missing Enzyme & Location: Glutaryl-coenzyme A dehydrogenase found in the mitochondria; liver, kidney and fibroblasts and leukocytes- catalyzes the oxidative decarboxylation of glutaryl-CoA to crotonyl-CoA

MS/MS profile: C5-DC (glutaryl carnitine)- elevated- can be missed in some patients

Prenatal testing: Yes. Enzyme activity in CVS and amniocytes

Miscellaneous Information:

Neuroradiographic findings of frontal-temporal atrophy and/or arachnoid cysts before the onset of symptoms. Infants with GA I are prone to suffer acute subdural hemorrhages and retinal hemorrhages after minor head trauma, i.e. commonly around the first birthday when starting to walk. This can be misdiagnosed as child abuse. In this population, 20-30% of patients have “chronic” subdural effusions and hematomas identified on neuroimaging studies; these are always found in the presence of atrophy and extra cerebral fluid. At least 2 patients with GA I have developed rhabdomyolysis after fairly mild infections.

Prepared for the NW Regional Newborn Screening Program by Sara Copeland MD, Judith Tuerck RN MS and Lorinda Paradise at OHSU in Portland, OR.

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