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Glutaric Acidemia-Type I (GA I)

Background

Glutaric Acidemia, Type I (GA I), was first described in 1975. The disease is caused by a genetic deficiency of the enzyme, Glutaryl-CoA Dehydrogenase (GCD), which leads to the buildup of Glutaric acid in the tissues and its excretion in the urine of affected patients. GCD is involved in the catabolism of the amino acids, Lysine, Hydroxylysine, and Tryptophan.

Over 200 cases of GA I have been reported in the medical literature. GA I is one of the most common organic acidemias and has an estimated incidence of about one in 50,000 live births. Because of the initial slow progression of clinical symptoms, GA I is frequently undiagnosed until an acute metabolic crisis occurs.

Clinical

Newborns with GA I may appear normal at birth or have macrocephaly. Development is typically normal during the first year of life until the infant experiences an acute encephalopathic crisis brought on by an intercurrent illness. Symptoms are characterized by metabolic acidosis, dystonia, athetosis, and seizures. The patient is often left with permanent dystonia and long-term loss of motor function. Neurologic recovery is rare and incomplete. As an alternate presentation, an affected infant may be delayed in achieving early motor milestones and appear irritable, jittery, hypotonic, and have impaired voluntary movements. This may progress as a gradual neurological disorder with preservation of mental abilities. Both presentations involve destruction of the caudate and putamen resulting in the movement disorder typical of GA I. Affected patients have a very high risk for neurologic problems before age five.

Testing

Newborn screening using tandem mass spectrometry of the heel stick dried blood spot identifies patients with GA I by the presence of glutaric acid covalently bound to carnitine (C5-dicarboxylic acylcarnitine, C5-DC). This permits the earliest possible diagnosis and initiation of treatment for presymptomatic patients. In acutely ill patients, large amounts of glutaric acid can be detected in blood and urine by organic acid analysis. Analysis of the urine for abnormal organic acids in a suspected patient may reveal glutaric acid, 3-hydroxyglutaric acid (which is pathognomonic for GA I), and possibly glutaconic acid. These organic acids may be missing, however, in patients who are not acutely ill, in which case acylcarnitine analysis or enzymatic testing is preferred. GCD enzyme activity can be assayed in cultured fibroblasts, cultured amniocytes and chorionic villus (direct or cultured). Prenatal diagnosis has also been accomplished by finding elevated glutaric acid in amniotic fluid. DNA mutation analysis for prenatal diagnosis requires knowing the mutation(s) in the parents prior to testing. Free carnitine levels are often low and acylated carnitine levels are high at diagnosis. Plasma amino acids are usually normal and not helpful in diagnosis.

Several different gene mutations have been found to cause GA I. There has been no correlation of the DNA mutation with the clinical severity of the disorder for a given patient.

Treatment

Early, aggressive treatment prior to onset of clinical symptoms may prevent development of neurological damage. At the onset of any sickness or metabolic decompensation, prompt, vigorous initiation of IV fluids, including glucose and carnitine, with monitored administration of insulin, is recommended. Restriction of protein, i.e. Lysine and Tryptophan restriction, has not produced clear clinical benefits.

Because the diagnosis and therapy of GA I is complex, the pediatrician is advised to manage the patient in close collaboration with a consulting pediatric metabolic disease specialist. It is suggested that parents travel with a letter of treatment guidelines from the patient's physician.

Inheritance

This disorder most often follows an autosomal recessive inheritance pattern. With recessive disorders affected patients usually have two copies of a disease gene (or mutation) in order to show symptoms. People with only one copy of the disease gene (called carriers) generally do not show signs or symptoms of the condition but can pass the disease gene to their children. When both parents are carriers of the disease gene for a particular disorder, there is a 25% chance with each pregnancy that they will have a child affected with the disorder.

References

Goodman, S.I. and Frerman, F.E. Organic acidemias due to defects in Lysine oxidation: 2-ketoadipic acidemia and Glutaric Acidemia. In, The Metabolic and Molecular Basis of Inherited Disease. 8th Edition, 2001. Scriver, Beaudet, et al. McGraw-Hill. Chapter 95, pg. 2195 - 2204.

Lipkin, P.H., Roe, C.R., et al. A case of Glutaric acidemia type I: effect of riboflavin and carnitine. J Pediatrics 112:62, 1988.

Aamir, N., Eleleg, O.N., et al. Glutaric aciduria type I: Enzymatic and neuroradiologic investigations of two kindreds. J Pediatrics 114:983, 1989.