



State of CT Genetics Newborn Screening Program Health Care Provider Fact Sheet

Glutaric Acidemia Type II (GA II) or Multiple acyl-CoA Dehydrogenase Deficiency (MADD)

Introduction

Glutaric Acidemia Type II (GA II) or multiple acyl-CoA dehydrogenase deficiency (MADD), is an inherited disorder characterized by hypoketotic or nonketotic hypoglycemia and metabolic acidosis, pathologically by fatty degeneration of liver parenchymal cells, renal tubular epithelium, and myocardium, and biochemically by the accumulation of metabolites of compounds oxidized by enzymes that transfer electrons to electron transfer flavoprotein (ETF). In most cases the disorder is due to the deficiency of either ETF or electron transfer flavoprotein ubiquinone oxidoreductase (ETF-QO), but in some cases the disorder may be due to an as yet undefined abnormality in flavin metabolism or transport. Complete deficiency of ETF-QO is often associated with congenital anomalies, the most frequent and characteristic being cysts, and dysplasia of the kidneys. All forms of the disease are transmitted as autosomal recessive traits. Most patients with severe disease do not survive the first few weeks of life.

Clinical Features

Three different phenotypes that stay consistent within families:

Neonatal onset with congenital anomalies: Infants often premature, present during the first 24-48 hrs of life with hypotonia, hepatomegaly, hypoglycemia, metabolic acidosis, sweaty feet odor, kidneys are often palpably enlarged and cystic, facial dysmorphisms, rocker-bottom feet, muscular defects of the anterior abdominal wall and anomalies of the external genitalia (hypospadias and chordee). Virtually all die within the first week of life.

Neonatal onset without anomalies: Infants develop problems within the first few days of life with hypotonia, tachypnea, metabolic acidosis, hepatomegaly, hypoglycemia, and sweaty feet odor. The few who have survived beyond the first week of life have died within a few months usually with severe cardiomyopathy. A few others have been hypoglycemic as newborns and later developed typical episodes of Reye syndrome-like illness and have survived somewhat longer.

Mild or late onset is extremely variable in its course and age at presentation, but typically include episodes of Hypoketotic hypoglycemia and hepatic dysfunction. There is progressive lipid storage myopathy and carnitine deficiency and few had progressive extrapyramidal movement disorders similar to GAI. There are reports of asymptomatic adults.

Diagnosis

Newborn screening—Tandem mass spectrometry: C4; C5; C6; C8; C10

Confirmation— a second sample may be requested or follow up testing will be done at the Metabolic Treatment Center at Yale or UCONN Genetics.

Situations that risk metabolic decompensation

Metabolic decompensation can be triggered by the catabolic processes that occur in the course of an infection, after an immunization or with a prolonged period of fasting. Lethargy, vomiting, apnea, or seizures are typical clinical features with or without hypoglycemia. Infants may be more subject to sudden death than older children.

Monitoring

Clinical observation is the most important tool for monitoring patients with GA II. They should be observed for recurrent vomiting, refusal to eat, increased lethargy, apnea or seizures. In these

situations, immediate evaluation in the emergency room is necessary. In situations of metabolic decompensation hypoglycemia can develop, but a normal blood glucose does not rule out metabolic instability and should never be a reason to delay therapy. It is also important for the primary care provider and the Metabolic Treatment Center to develop an on-going collaborative relationship in caring for these patients.

Treatment

- Treatment of the severe neonatal presentations is not effective. Mainstay therapies include avoidance of fasting, a diet low in fat and protein and high in carbohydrate. This diet prescription will be individualized to the patient by the metabolic team at the treatment center the patient attends. Riboflavin supplementation in the milder cases has been curative in some cases. Additional supplements of glycine and L-carnitine have been used. A long lasting carbohydrate source, such as cornstarch, may also be a helpful adjunct. Infants and children with GA II should have regularly scheduled visits at the Metabolic Treatment Center.
- Avoid fasting. Feed at regular intervals during the day and limit overnight fasting
- Should not go without food intake longer than 4 hours for the first 4 months of life; 6 hours for ages 4-8 months; and no longer than 8 hours thereafter
- **The Metabolic Treatment Center will set a patient's diet prescription.**
- If the child is vomiting or refuses to eat, (s)he needs to be taken to an emergency room for IV administration of 10% dextrose.
- An emergency protocol, provided by the Metabolic Treatment Center, contains basic information about the disorder, necessary diagnostic investigations and guidelines for treatment.

Illness

- Any illness can potentially lead to metabolic decompensation
- Prevention and/or early intervention is of particular importance
- Care should be coordinated by the Metabolic Treatment Center

Immunization

- Immunizations must be kept current.

Surgical/surgical procedures

- Discuss any plans for surgical and dental procedures with the Metabolic Treatment Center.
- A surgical procedure constitutes a potentially catabolic situation and preoperative fasting should be avoided with 10% dextrose being started preoperatively and continuing postoperatively until the child is eating and drinking well. Any procedure requiring anesthesia should be done at a hospital with a metabolic service.

Growth and development

- It is crucial to closely monitor all growth parameters on a regular basis.
- In cases with neurological deficits, the child should be referred to an early intervention program and developmental progress closely monitored by both the metabolic team and the primary care provider.



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