Beta-Ketothiolase Deficiency (Mitochondrial Acetoacetyl CoA Thiolase Deficiency (BKT))

Introduction
Beta-kethothiolase deficiency is a rare metabolic disorder of branched chain amino acids, which is characterised by an increased plasma glycine level, metabolic acidosis and ketosis. The clinical manifestations range from an asymptomatic course to severe life threatening ketoacidosis with coma and cardiomyopathy. The attacks are usually precipitated by high protein ingestion or by systemic infections. There is abnormal urinary excretion of 2-methyl-3-hydroxybutyric acid, tiglylglycine and in some cases also 2-methylacetoacetic acid and butanone (3,5,6).

Other names for this disorder: Mitochondrial Acetoacetyl CoA Thiolase Deficiency, 2-Methylacetoacetyl CoA Thiolase Deficiency, 3-Ketothiolase Deficiency, Acetoacteyl-CoA Thiolase Deficiency, Beta Ketothiolase Deficiency, Ketone Utilization Disorder.

This autosomal recessive disorder is an inborn error of isoleucine catabolism characterized by urinary excretion of 2-methyl-3-hydroxybutyric acid, 2-methylacetoacetic acid, tiglylglycine, and 2-butanone.

The onset of symptoms occurs in late infancy or childhood. The mean age at presentation is 15 months (range 3 days to 48 months). There are documented cases of asymptomatic patients with enzyme deficiency. Frequency of decompensation attacks falls with age and is uncommon after the age of 10. Clinical outcome varies widely with a few patients suffering severe psychomotor retardation or death as a result of their initial attack and others with normal development and no episodes of acidosis. Despite severe recurrent attacks, appropriate supportive care can result in normal development. Symptoms include intermittent episodes of severe metabolic acidosis and ketosis accompanied by vomiting (often hematemesis), diarrhea and coma that may progress to death. There is great clinical heterogeneity between patients. Infancy is the period of highest risk for decompensation. Death or neurologic complications can occur. Neurologic damage includes striatal necrosis of the basal ganglia, dystonia and/or mental retardation. Other symptoms include cardiomyopathy, prolonged QT interval, neutropenia, thrombocytopenia, poor weight gain, renal failure and short stature. If neurologically intact, patients are normal between episodes.

Diagnosis
Newborn screening—Tandem mass spectrometry: C5:1
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 infections, after an immunization, increased physical activity or with a prolonged period of fasting.
Monitoring

- Clinical observation is the most important tool for monitoring patients with BKT. It is important for the primary care provider and the Metabolic Treatment Center to develop an on-going collaborative relationship in caring for these patients.
- Carefully assess infants presenting with unexplained vomiting for signs of metabolic acidosis and ketosis. Urinalysis is particularly important in this regard since neonates normally do not excrete large quantities of ketones.

Treatment

- Acute management of the ketoacidosis is supportive with IV glucose and bicarbonate.
- Bicarbonate therapy is often required long term.
- Protein rich diets and ketogenic diets should be avoided.
- Carnitine supplementation can be used.
- The family should monitor urinary ketones to be alert for impending metabolic crisis.

Illness

- Any illness can potentially lead to metabolic decompensation.
- Prevention and/or early intervention is of particular importance.
- Consult with the Metabolic Treatment Center within 24 hours of the onset of the illness.

Immunization

- Immunizations must be kept current.

Surgical/surgical procedures

- Discuss any plans for surgical and dental procedures with the Metabolic Treatment Center.
- 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, development, and biochemical parameters on a regular basis.
- With early diagnosis and treatment, apparently normal development occurs.
- 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.

860-509-8081

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