Defects of Fatty Acid Oxidation and Urea Cycle Disorders in Children

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Medium-chain acyl-CoA dehydrogenase deficiency is common among the defects of fatty acid oxidation. Affected individuals present with acute hypoketotic hypoglycemia and mild hyperammonemia. Diagnosis is made through positive newborn screening, and treatment is mainly preventive. Urea cycle disorders are genetic defects. Common symptoms include vomiting, lethargy, seizures, and respiratory alkalosis. Diagnosis is through molecular genetic testing. Treatment aims to reduce ammonia concentration in plasma. Acute episodes can be prevented through a dietary restriction of protein.

Definition and Introduction

A genetic defect in the production or utilization of any enzyme involved in fatty acid oxidation results in disorders of fatty acid oxidation.

Examples of such genetic defects include:

- Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)
- Mitochondrial trifunctional protein deficiency
- Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency
- Very-long-chain acyl-coenzyme A dehydrogenase deficiency

Medium-Chain Acyl-CoA Dehydrogenase Deficiency

This disorder results from an inability of medium-chain fatty acids to be converted into acetyl-CoA. Depending on the population, the incidence for MCAD is 1/4,000 to 1/17,000.

Signs and Symptoms

Symptoms of MCAD present in early childhood and include the following:

- Acute hypoketotic hypoglycemia (seizures or coma)
- Mild hyperammonemia
- Liver dysfunction

If not exacerbated by a stressful metabolic condition, some patients may never exhibit any symptoms of MCAD, while in others the first manifestation of the disorder may be death.

The following symptoms are characteristic of MCAD:

- Lethargy
- Seizures
- Coma
- Hypoketotic hypoglycemia triggered by a minor illness

Genetics

MCAD is an autosomal-recessive disorder caused by mutations in the ACADM gene, which codes for a protein of 421 amino acids.

Diagnosis

Diagnosis is made through positive newborn screening for low carnitine levels using tandem mass spectrometry.

Prognosis

MCAD has an excellent prognosis if identified before the onset of symptoms.

Treatment

- Supplement with IV glucose (D10 at 1.5 × maintenance)
- Avoid prolonged fasting
- Eat starchy foods before bedtime
- Consume a low-fat diet
- Eat nutrients that are high in carbohydrates (every 2–6 hours)

Complications

MCAD deficiency can lead to breathing difficulties, seizures, brain damage, hepatic impairment, coma, and death.

Urea Cycle Defects

Urea cycle defects result from genetic inadequacies in the enzymes of the urea cycle. These genetic mutations cause enzyme and transporter deficiencies in the urea cycle. Affected individuals cannot consume more than the minimum daily requirement of amino acids; if they do, the ammonia produced will not be converted into urea, and they are likely to experience hyperammonemia.

Types

- Ornithine transcarbamoylase deficiency
- Argininosuccinic aciduria
- Hyperornithinemia, hyperammonemia, homocitrullinuria syndrome
- N-acetylglutamate synthase deficiency
- Argininemia
- Carbamoyl phosphate synthetase deficiency
- Citrullinemia

Argininemia and argininosuccinic aciduria usually do not present with elevated ammonia.

Signs and Symptoms

Neonatal Period

In patients with a severe disorder, symptoms appear typically after the first 24 hours of life.

Clinical presentation includes the following:

- Irritability and refusal to feed
- Vomiting
- Lethargy
- Seizures
- Floppiness
- Respiratory alkalosis
- Coma

These signs and symptoms are sometimes misdiagnosed as Reye’s syndrome or sepsis.

Childhood

Mild and moderate cases of urea cycle defects present in early childhood.

Clinical presentation includes the following:

- Failure to thrive
- Excessive crying
- Agitation
- Self-injurious behaviors
- Refusal to eat high-protein foods
- Lethargy
- Delirium

If the condition remains undiagnosed, hyperammonemia coma can occur, leading to death.

Adulthood

Individuals with mild deficiencies may not be diagnosed during childhood.

Symptoms include:

- Slurred speech
- Disorientation
- Confusion
- Agitation
- Delirium
- Lethargy
- Stroke-like symptoms
- Psychiatric issues such as bipolar disorder and schizophrenia

Symptoms in mild cases are observed following an episode of viral illness, excessive exercise, use of drugs such as valproic acid, and childbirth.

Diagnosis

Molecular genetic testing and the measurement of enzyme activity are used to diagnose this condition.

Indications for urea cycle defects include the following:

- Ammonia concentration in plasma ≥ 150 µmol/L
- Normal anion gap
- Normal plasma glucose concentration

Management

Dialysis and hemofiltration reduce ammonia concentration in plasma. Excretion of excess nitrogen is achieved through an alternative pathway:

- Arginine hydrochloride (IV)
- Sodium benzoate (IV)
- Sodium phenylacetate (IV)

Physiologic stabilization

- IV fluids
- Cardiac pressors

Other

Other management options include eliminating protein from the diet for 12–24 hours and routine monitoring.

Prevention of Acute Episodes

- Dietary restriction (protein)
- Avoidance of valproic acid
- Consumption of specialized formulas
- Avoidance of prolonged fasting

Complications

Untreated high serum ammonia due to urea cycle defects may cause uremic encephalopathy, fits, coma, and death.

References

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