

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 to Defects of Fatty Acid Oxidation

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 are as follows:

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

Medium-chain Acyl-CoA Dehydrogenase Deficiency (MCAD)

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 1:4000 to 1:17,000.

Signs and symptoms of MCAD

Symptoms of MCAD present in early childhood:

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

If not encountered by a stressful metabolic condition, some individuals may survive even without any manifestation of MCAD, while others may have died as the first manifestation of MCAD.

Individuals with the following symptoms are suspected of MCAD:

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

Genetics

MCAD is an autosomal recessive disorder.

Gene involved

ACADM

This gene codes for a protein of 421 amino acids.

Diagnosis of MCAD

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

Prognosis of MCAD

Medium-chain acyl-CoA dehydrogenase deficiency has an excellent prognosis if identified before the onset of symptoms.

Treatment of MCAD

- Supplement with IV Glucose (D10 at 1.5× maintenance)
- Avoid prolonged fasting
- Starch at bedtime
- Low-fat diet
- Use of nutrients that are high in carbohydrates (every 2-6 hours)

Complications

MCAD deficiency may lead to breathing difficulty, 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 enzymes and transporters deficiencies used in the urea cycle. The major issue associated with the affected individuals is that they cannot consume amino acids more than the minimum daily requirement. Otherwise, the ammonia produced will not be converted into urea. These individuals are most likely to experience hyperammonemia.

Types of Urea Cycle Defects

- Ornithine transcarbamoylase deficiency OTC
- 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 of Urea Cycle Defects

Neonatal period:

In the case of severe disorder, symptoms appear typically after the first 24 hours of life. Following is the clinical presentation:

- Baby is irritable and refuses the feed
- Vomiting
- Lethargy
- Seizures
- Floppiness
- Respiratory alkalosis
- Comma may occur

These signs and symptoms can commonly be misdiagnosed as Reye's syndrome and sepsis.

Childhood:

Mild and moderate cases of urea cycle defects present in early childhood. Following are the symptoms:

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

- Lethargy
- Delirium

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

Adulthood:

Individuals with mild deficiencies may not be diagnosed during childhood. Symptoms of mild deficiencies are:

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

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

Diagnosis

Molecular genetic testing and the measurement of enzyme activity.

Indication for urea cycle defects:

- Ammonia concentration in plasma $\geq 150 \mu\text{mol/L}$
- Normal anion gap
- Normal plasma glucose concentration

Management of Urea Cycle Defects

To reduce ammonia concentration in plasma

- Dialysis
- Hemofiltration

For excretion of excess nitrogen through an alternative pathway:

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

Physiologic stabilization:

- I/V fluids
- Cardiac pressors

Others:

Other management options are the discontinuation of protein diet for 12 to 24 hours or individuals with urea cycle disorders need routine monitoring by an experienced physician.

Prevention of acute episodes

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

Complications

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

References

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