Urea Cycle Disorders

Disorders of the urea cycle *(small Krebs cycle, ornithine cycle, ureosynthetic cycle)* form a group of enzymatic disorders, which result in the accumulation of nitrogen in the form of ammonia, which is very toxic to the body and causes irreversible brain damage.

The clinical manifestation of these diseases occurs usually during the first days of life. Hyperammonemia causes cramps, vomiting, and eventually coma. In older children, these disorders most often manifest as psychomotor retardation, failure to thrive, vomiting, behavioral disorders, recurrent cerebral ataxias, and headaches.

It is necessary to monitor the level of ammonia in the blood in every patient with neurological symptoms of unknown origin. The frequency of urea cycle disorders is approximately 1:30,000.[1][2]

Pathogenesis

The urea cycle serves to excrete excess nitrogen (ammonia) in the form of urea. Urea is non-toxic, freely soluble in water, and diffusible. Urea is the main organic component of urine.

If the urea cycle is disrupted due to an enzymatic defect, hyperammonemia develops, amino acids accumulate behind the enzyme block (substrate accumulation) and, conversely, the concentration of amino acids in front of the enzyme block decreases (product deficiency).

Plasma glutamine levels are also usually elevated. This is due to the fact that in this case an alternative route of ammonia conversion is used: it is used as a substrate for *glutamine synthetase*, whereby it is combined with glutamate to form glutamine. Increased glutamine content in astrocytes leads to **cerebral edema** due to its osmotic effect.

In the case of the accumulation of carbamoyl phosphate, orotic acid is formed, which is an important diagnostic marker. It is increased in disorders of all enzymes in the urea cycle except CPS1 since carbamoyl phosphate is not formed to begin with.[2]

Classificiation

Includes 5 inherited disorders:

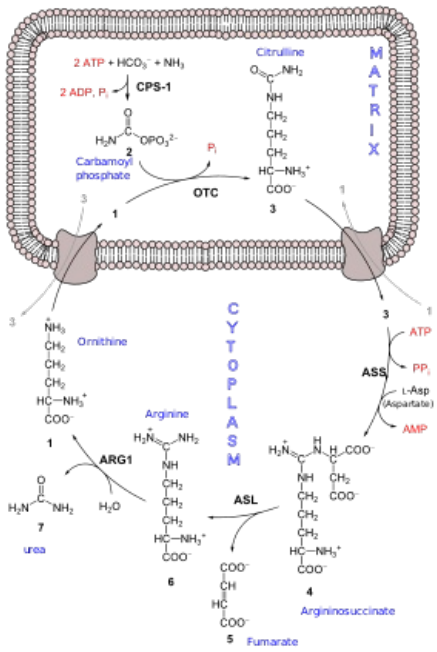
	affected enzyme	location	type of inheritance	incidence	OMIM	links
Hyperammonemia type I	carbamoyl phosphate synthetase (CPS1)	mitochondria	AR	rare (about 24 cases)	#237300 (http://omim.org/entry/237300)	[1] (http://www.metagene.de/program/d.prg?mp=CARBAMOYL%20PHOSPHATE%20SYNTHETASE%20DEFICIENCY%20(CPS))
Hyperammonemia type II	ornithine carbamoyltransferase (OTC)	mitochondria	X-linked, manifestations may also be present in heterozygous girls		#311250 (http://omim.org/entry/311250)	[2] (http://www.metagene.de/program/d.prg?mp=ORNITHINE%20TRANSCARBAMYLASE%20DEFICIENCY%20(OTC))
Citrullinemia	arginine succinate synthetase (ASS)	cytosol	AR	1:70 000–1:100 000	#215700 (http://omim.org/entry/215700)	[3] (http://www.metagene.de/program/d.prg?id_d=92)
Argininosuccinic aciduria	arginine succinate lyase (ASL)	cytosol	AR	1:70 000–1:100 000	#207900 (http://omim.org/entry/207900)	[4] (http://www.metagene.de/program/d.prg?mp=ARGININOSUCCINIC%20ACIDURIA%20(ASL))
Argininemia	arginase (ARG1)	cytosol	AR	rare (50 cases)	#207800 (http://omim.org/entry/207800)	[5] (http://www.metagene.de/program/d.prg?mp=ARGININEMIA.%20HYPERARGININEMIA,%20ARGINASE%20DEFICIENCY)

Clinical picture

Urea cycle disorders usually occur in 2 forms - early and late.

Early forms manifest shortly after birth. If not detected as soon as possible, the neonate will enter a hyperammonemic coma and experience metabolic acidosis, liver failure, convulsions, and cerebral edema.

Late forms are manifested by anorexia, vomiting, failure to thrive, hypotension, and disorders of psychomotor development.



Urea cycle

Hyperammonemia (type I)

It is a **carbamoyl phosphate synthetase** defect that occurs in two forms: **severe** (lethal neonatal) and **mild** with later onset.

The lethal neonatal form is manifested by severe brain damage, hyperammonemic coma, and ketoacidosis. In the **milder form**, hyperammonemic coma, Reye-like syndrome, vomiting, hypotension, failure to thrive, and psychomotor retardation may occur.[3]

In the analysis of the laboratory examination, we find **low concentrations of arginine and citrulline and high concentrations of glutamine**. In contrast, uracil and orotic acid are normal.

Citrullinemia (type I)

It is an **arginine succinate synthase** defect occurring in two forms. The first is **neonatal**, manifested by hyperammonemic coma and lactic acidosis. The second form is the **chronic juvenile form**, whose symptoms are anorexia, vomiting, hypotension, growth and psychomotor retardation, and convulsions.

We distinguish two more types of citrullinemia. **Type II** is characterized by a deficiency of the mitochondrial transporter aspartate and glutamate (citrin), resulting in an intramitochondrial aspartate deficiency. **Type III** is characterized by a partial arginine succinate synthetase deficiency with high residual enzyme activity.[4]

In the laboratory, we find low concentrations of arginine, but **high concentrations of citrulline and glutamine, and uracil and orotic acid are increased.**

Argininosuccinic aciduria

It is an **arginine succinate lyase** defect that occurs in two forms, early and late. **The early form** manifests as a severe hyperammonemic coma shortly after birth and is often **fatal**. In the **late form**, we can observe hypotension, failure to thrive, loss of appetite, chronic vomiting, and behavioral disorders during childhood. Other manifestations may include hepatomegaly and brittle hair (*trichorrhexis nodosa)*.[5]

In the laboratory, we find a **low concentration of arginine and increased concentrations of glutamine and citrulline**, and **an increase in the concentration of orotic acid and uracil** in the urine.

Argininemia

It is an **arginase I** defect, the symptoms of which include spastic diplegia, epilepsy, psychomotor retardation, hyperactivity, irritability, inconsolable crying, anorexia, vomiting, and rarely symptomatic hyperammonemia progressing to coma.

We show **hyperargininemia** in the laboratory and **increased** urinary **excretion of orotic acid**. The leading symptom is **hyperammonemia**.

If we examine the ABB, we first find respiratory alkalosis and later metabolic acidosis.

Another important indicator of these disorders is the examination of **amino acids in plasma** (chromatography), where in the results we find increased concentration of glutamine, glutamic acid, and little arginine (except in argininemia), further increased amino acid concentration before enzymatic defect and decreased amino acid concentrations after the defect (e.g., little citrulline and a lot of arginine). Orotate → OTC - as with each enzyme block.

Orotic acid in the urine is elevated in disorders of all enzymes except CPS1.

We perform enzyme activity assays using liver biopsies. Another important examination method is the searching for mutations[2].

Differential diagnosis of hyperammonemia

Hyperammonemia can be either congenital or acquired.

Congenital defects include urea cycle disorders, organic aciduria, fatty acid transport or oxidation disorders, hyperinsulinism, and hyperammonemic syndrome.

We include Reye's syndrome, liver failure of other etiology, transient hyperammonemia of the newborn (it is mainly in LBWI). Treatment is performed with the help of valproate.[2]

Therapy

First aid consists of ensuring an anabolic state (high intravenous doses of glucose with insulin, high-calorie parenteral nutrition) and detoxification. **Sodium benzoate** activates alternative pathways of nitrogen excretion. **Phenylbutyrate**, which is metabolized to **phenylacetate**, ensures the binding of glutamine and allows it to be excreted by the kidneys. In case of impaired consciousness, an elimination method (hemodialysis, hemodiafiltration) must be used to reduce ammonia. We can also **substitute certain amino acids** (usually arginine and citrulline - valid only in selected defects).

Lifetime **protein intake** must be **reduced** to 0-1.2 g / kg / day and must be substituted with essential AMK mixtures. Liver transplantation is required for severe metabolic disorders.[2]

Prognosis

With early therapy (except in severe forms of OTC), prognosis may be good. With the development of severe hyperammonemic coma (usually over 300 µmol / L ammonia, compared to the physiologic concentration of 50 to 70 µmol / L) in neonatal age, there is a high risk of disability.[2]

Related articles

- Urea cycle
- Hereditary disorders of amino acid metabolism
- Hereditary disorders of carbohydrate metabolism
- Hereditary disorders of fat metabolism

Reference

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