Disorders of pyrimidine metabolism

The disorders of pyrimidine metabolism mainly affect the reactions of **de novo synthesis** and **pyrimidine catabolism**. Pyrimidine biosynthesis takes place in the cytosol. Carbamoyl phosphate reacts with aspartate to form carbamoyl aspartate, dihydroorotate, orotate, OMP (orotidyl monophosphate) and UMP (uridine monophosphate). Catabolism produces β-aminoisobutyrate and β-alanine, from which the citric acid cycle intermediates are formed.

Disorders of pyrimidine synthesis

UMP synthase deficiency (Orotic aciduria)

This is an AR inherited disorder. UMP synthase has two enzymatic activities as orotate phosphoribosyltransferase (OPRT) and orotate decarboxylase (ODC). Blockade in the synthesis of pyrimidines leads to the accumulation of orotate in body fluids, and with its increased excretion crystalluria can occur. At the same time, there is a pyrimidine deficiency for DNA synthesis, resulting in cell division disorders and megaloblastic anaemia which is unresponsive to treatment with iron, vitamin B12 or folic acid, as the disorder is due to insufficient DNA synthesis due to a lack of pyrimidine bases.

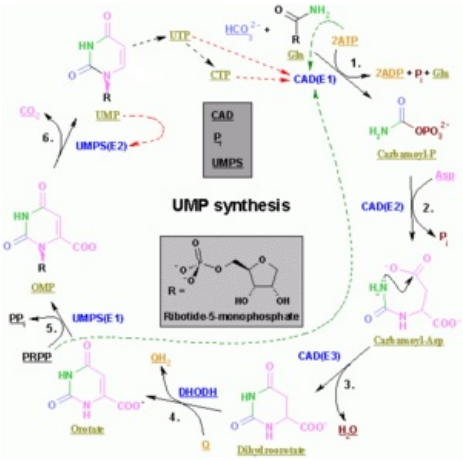
Growth disorders, psychomotor retardation, leukopenia and malaise appear. It is treated with uridine. In this case, it is also possible to make a prenatal diagnosis.

Pyrimidine degradation disorders

Dihydropyrimidine dehydrogenase (DPD) deficiency

This is an AR inherited disorder. Impaired conversion of uracil and thymine to dihydrouracil and dihydrothymine leads to accumulation of uracil and thymine in body fluids. Clinically, complete DPD deficiency occurs in children and is accompanied by epilepsy, mental retardation and microcephaly.

The second clinical form is partial deficiency, which is only discovered in connection with treatment with 5-fluorouracil (for tumours), which is not sufficiently degraded (partial DPD deficiency) and is toxic to the patient. It is manifested by neutropenia, stomatitis and neurological symptoms. Decreased production of the neurotransmitter β-alanine, which is a product of pyrimidine catabolism, may be important in the context of neurological symptoms. Treatment in the pediatric form is not available, and in case of partial deficiency due to treatment with 5-fluorouracil, we will change the chemotherapeutic. Even in this case, it is possible to perform prenatal diagnosis.



Pyrimidine metabolism

Dihydropyrimidinase deficiency

The enzyme dihydropyrimidinase (DHP) cleaves dihydrouracil to β-ureidopropionate, and dihydrothymine to β-ureidoisobutyrate. Dihydrouracil and dihydrothymine mean less uracil and thymine in urine. Symptoms are similar to DPD deficiency and the **treatment is unknown**.

Thymidine phosphorylase deficiency

This deficiency has been found in patients with MNGIE (mitochondrial neurogastrointestinal encephalomyopathy). Nucleotide accumulation is likely to lead to mtDNA replication disorders.

Clinical signs and laboratory findings show lactic acidosis and aciduria and markedly increased urinary and blood excretion of thymidine.

Links

Related articles

- Disorders of purine metabolism

Literature

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