Defect in pterin-4 alpha-carbinolamine dehydratase

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Abstract

Dehydratase deficiency is one of the etiologies of hyperphenylalaninemia due to tetrahydrobiopterin deficiency. However pterin-4 alpha-carbinolamine dehydratase (PCD) deficiency is a mild pathological abnormality, except for the risk of induced hyperphenylalaninemia. In some cases, the following signs have been noted: hypotonia, irritability that can be seen on the EEG, and slow acquisition of psychomotor skills. It is diagnosed when the 7-biopterin isomer (primapterin) is - usually fortuitously - found in the biological fluids of an infant with hyperphenylalaninemia. Management is mainly based on dietary and restricted phenylalanine intake.

Keywords

hyperphenylalaninemia, tetrahydrobiopterin deficiency, dehydratase deficiency, restricted phenylalanine intake

Disease name and synonyms

Pterin-4 alpha-carbinolamine dehydratase (PCD) deficiency,
Primapterinuria.

Excluded diseases

Other hyperphenylalaninemias (phenylketonuria, mild hyperphenylalaninemia, etc.), other tetrahydrobiopterin deficiencies (GTP-cyclohydrolase (GTPch), 6-pyruvoyl-tetrahydropterin synthase (PTPS), dihydropteridin reductase (DHPR)).

Diagnosis criteria/definition

This condition was described following the systematic search for tetrahydrobiopterin deficiency in a hyperphenylalaninemic infant. The presence in body fluids of 7-biopterin (an isomer of 6-biopterin) defines the disorder. This enzymatic deficit results in mild hyperphenylalaninemia; the perturbation of tetrahydrobiopterin recycling does seem not to be sufficient to induce the neurological impairment seen in other tetrahydrobiopterin deficiencies.
Differential diagnosis
Although the incidence of tetrahydrobiopterin deficiencies remains low, it is important to be sure that patients with hyperphenylalaninemia are not tetrahydrobiopterin deficient so that a good response to a low-phenylalanine diet can be confidently predicted. It is recommended that all infants with hyperphenylalaninemia be screened for defects in tetrahydrobiopterin metabolism even in the absence of neurological symptoms, and regardless of the degree of hyperphenylalaninemia (mild, transient, persistent,...).

Prevalence
Nineteen cases are known (6% of whom are tetrahydrobiopterin-deficient patients) (in France: 6 cases).

Clinical description
The absence of clinical signs characterizes this form of tetrahydrobiopterin deficiency. Although some patients experience mild tremors of the upper limbs after stimulation and tonus abnormalities have been observed during the neonatal period, neurological development was normal with dietary control of blood phenylalanine.

Management including treatment
Control of the hyperphenylalaninemia seems necessary. Tetrahydrobiopterin (7-10 mg/kg/d) has been used for that purpose for a few months.

Diagnostic methods
This form of hyperphenylalaninemia is characterized by the presence of 7-biopterin (primapterin) which is excreted in equal amounts with 6-biopterin, the natural isomer. At birth, the neopterin/biopterin ratio was elevated indicating that biopterin levels were in the low/normal range. With increasing age, the pterin pattern gradually normalized, except that 7-biopterin remained present at a high concentration. Cerebrospinal fluid (CSF) neurotransmitter levels are normal.

The tetrahydrobiopterin-loading test (2-20 mg/kg) results in a decrease of blood phenylalanine, thereby confirming that the hyperphenylalaninemia is indeed tetrahydrobiopterin-dependent.

Genetic counseling
Primapterinuria occurs in both sexes and demonstration of slightly increased 7-biopterin excretion in both parents and one of the two brothers in a family, indicated that the condition is autosomal recessive. Nine mutations of the gene (PCBD) have been described recently.

Antenatal diagnosis
Prenatal diagnosis is not recommended since there is no proof that the enzymatic defect is harmful.

References

http://www.orpha.net/data/patho/GB/uk-pcd.pdf