Defect in dihydropteridine reductase

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Abstract

Dihydropteridine reductase (DHPR) deficiency, an autosomal recessive genetic disorder, is one of the causes of malignant hyperphenylalaninemia due to tetrahydrobiopterin deficiency. Not only does tetrahydrobiopterin deficiency cause hyperphenylalaninemia, it is also responsible for defective neurotransmission of monoamines because of malfunctioning tyrosine and tryptophan hydroxylases, both tetrahydrobiopterin-dependent hydroxylases. DHPR deficiency should be suspected in all infants with a positive neonatal screening test for phenylketonuria, especially when hyperphenylalaninemia is moderate. DHPR activity can be measured by means of a technique adapted to dry blood samples. When left untreated, DHPR deficiency leads to neurological signs at age 4 or 5 months, although clinical signs are often obvious from birth. The principal symptoms include: psychomotor retardation, tonicity disorders, drowsiness, irritability, abnormal movements, hyperthermia, hypersalivation, and difficult swallowing. The treatment attempts to bring phenylalaninemia levels back to normal (diet with restricted phenylalanine intake or prescription of tetrahydrobipterin) and to restore normal monoaminergic neurotransmission by administering precursors (L-dopa/carbidopa and 5-hydroxytryptophane). Folic acid intake prevents progressive deficits of cerebral folates, while antifolates, such as cotrimoxazole are dangerous.

Keywords

tetrahydrobiopterin deficiency, malignant hyperphenylalaninemia, defective neurotransmission, folic acid intake

Disease name and synonyms

• Dihydropteridine reductase (DHPR) deficiency (EC.1.6.99.7),
• Tetrahydrobiopterin deficiency,
• Malignant hyperphenylalaninemia.

Excluded diseases

Other hyperphenylalaninemas (phenylketonuria (PKU), mild hyperphenylalaninemia), other tetrabhydrobipterin deficiencies (GTP-cyclohydrolase (GTPch) deficiency, 6-pyruvyl-
tetrahydropterin synthase (PTPS) pterin-4 alpha-carbinolamine dehydratase (PCD)

Diagnostic criteria / definition
DHPR deficiency is one of the etiologies of "malignant hyperphenylalaninemia" which results from tetrahydrobiopterin deficiency. In addition to being hyperphenylalaninemic, patients lacking tetrahydrobipterin are deficient in the neurotransmitters whose syntheses depend on the normal activity of tetrahydrobipterin-dependent tyrosine and tryptophan hydroxylases (EC.1.14.16.2 and EC.1.14.16.4).

Differential diagnosis
Although the incidence of tetrahydrobipterin deficiencies remains low, it is important to be sure that patients with hyperphenylalaninemia are not tetrahydrobipterin deficient so that good results with a low phenylalanine diet can be confidently predicted. It is recommended to that all infants with hyperphenylalaninemia be screened for defects in tetrahydrobipterin metabolism even in the absence of neurological symptoms, and regardless of the degree of the hyperphenylalaninemia (mild, transient, persistent, etc.)

Prevalence
DHPR deficiency is one of the most frequent conditions resulting in tetrahydrobipterin deficiency: 110 cases are known (32% of them are tetrahydrobipterin-deficient patients), in France: 8 cases in 6 families, Consanguinity exists in 2/3 of cases and explains the higher prevalence in some countries (Turkey, southern Italy, North Africa, etc).

Clinical description
The median age at which clinical signs became evident was 4-5 months, but symptoms do not necessarily correlate with age at diagnosis, even in a given family. However, during the neonatal period, abnormal signs (poor sucking, fewer spontaneous movements, floppy baby) can be observed. The common symptoms were: mental retardation, convulsions, disturbances of tonicity and posture, drowsiness, irritability, abnormal movements, recurrent hyperthermia without infection, hypersalivation, swallowing difficulties. Diurnal fluctuation of alertness and neurological symptoms are often reported. Microcephaly (head circumference less than the mean minus 2 standard deviation for age) is observed in 1/3 of the cases. The neuroradiological and electrophysiological abnormalities were often less severe than would be expected from the clinical picture. EEG tracings and changes with age are not specific. Considering data obtained before 1 year of age, EEG was normal in 38% of DHPR-deficient patients, paroxysmal activity (hypsarrhythmia, sharp waves, epileptic discharges) was observed in 46%. Neuroanatomical investigations (CT scan & MRI) showed frequent and rather early brain atrophy. DHPR deficiency may produce progressive intracranial calcifications, most evident in the basal ganglia but also present in other areas of cerebral white and gray matter. These calcifications are thought to arise as a result of the decrease of cerebral folic acid. Some authors suggest that a partial deficiency of DHPR activity may also exist. That could explain a few reports of patients who had other manifestations.

Management including treatment
The goal is to control hyperphenylalaninemia by dietary restriction of phenylalanine intake or tetrahydrobiopterin administration, and to restore neurotransmitter homeostasis by oral administration of amine precursors L-dopa and 5 hydroxy-tryptophan (5HT). Carbidopa, an inhibitor of peripheral aromatic aminoacid decarboxylase, enables the lowering of the therapeutic dose of L-dopa.

The doses usually given are L-dopa/carbidopa : 5-10 mg/kg body weight (b;w)/day, 5HT: 5-10 mg/kg bw/day. However, doses can vary, and indeed have to be tailored for each individual. The daily neurotransmitter dose is usually divided into three equal proportions. However, diurnal fluctuations are often observed and require changes in the schedule of drug administration. The optimal dose should be adjusted to the requirements of each patient with monitoring for adverse effects and possible disappearance of neurological symptoms when they exist. Unfortunately, no biochemical parameters measurable in the periphery (except hyperprolactinemia which is a good indicator of the hypothalamic dopamine deficiency) adequately monitor; consequently, analyzing of neurotransmitter metabolites in cerebrospinal fluid (CSF) represents the most direct way to evaluate its efficacy, at least from a biochemical point of view.

Although tetrahydrobipterin-deficient subjects exhibit higher dietary phenylalanine tolerance than classical phenylketonuria (PKU) patients, a factor limiting in the response to neurotransmitter precursor therapy might be the plasma phenylalanine fluctuations, which could alter the dose-effect relationships of these substances, by interfering with their membrane transport or by competitive inhibition of tyrosine and tryptophan hydroxylases. Blood phenylalanine has to be more strictly controlled than for other hyperphenylalaninemas, some patients on neurotransmitter treatment have developed
neurological problems with phenylalanine concentrations as low as 6 mg/dl. In contrast to PTPS deficiency, tetrahydrobiopterin therapy alone for DHPR deficiency does not seem feasible because sufficiently high amounts cannot be given in to maintain an adequate pool of tetrahydrobiopterin in the absence of the endogenous reducing system maintained by DHPR. The picture is also more complicated as a gradual folate deficit may occur within the central nervous system. A direct relationship between of folic acid administration and clinical improvement has been observed. On the contrary, folic acid (oxidized form) administration aggravates the symptoms. The adverse effect of cotrimoxazole has been shown. The potential danger of using other folate analogs is likely.

Diagnostic methods
The diagnosis has to be considered in all conditions with hyperphenylalaninemia. DHPR deficiency can be suspected from measurements of related metabolites in urine, blood and CSF; but it can be confirmed only by specific assay of the enzyme's activity. Owing to the lack of tetrahydrobiopterin, the absence of feedback inhibition of GTPch results in activation of pterin biosynthesis, which explains the high amounts of biopterin in body fluids. However and particularly in very young patients, the neopterin/biopterin ratio which is expected to be low, is close to values found in PKU patients. High CSF biopterin levels are also found. The distribution of CSF 5-hydroxyindolacetic acid (5-HIAA) and homovanillic acid (HVA) is similar to those observed in PTPS deficiency. The 5-HIAA decrease is more important than that of HVA and both metabolites decrease with age in parallel to normal control levels. Diagnosis of DHPR deficiencies also can be missed by a tetrahydrobiopterin-loading test, (2-20 mg/kg) and the persistence of hyperphenylalaninemia during the assay can be misinterpreted as phenylalanine hydroxylase (PAH) deficiency (PKU). The lack of efficacy of tetrahydrobiopterin administration on blood phenylalanine is presumably due to the dose of tetrahydrobiopterin, which is insufficient to maintain repeated cycles of hydroxylation. To overcome these diagnostic difficulties, DHPR measurement is strongly recommended. DHPR assay in erythrocytes of dried blood spots has been shown reliable for this purpose and is now used for detection of the disease.

Genetic counseling
DHPR deficiency is a genetic disorder with autosomal recessive inheritance, the disease occurs in both sexes and consanguinity is common. The gene (QDPR) has been located on chromosome 4q15.3 (7 exons), 26 mutations have been reported recently.

Antenatal diagnosis
The option of prenatal diagnosis is likely to be taken seriously, since the prognosis of these conditions is subject to much uncertainty. DHPR activity can be measured in amniocytes. DNA analysis can also be used.

References
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