Defect in pyruvoyl-tetrahydropterin synthase

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Abstract
6-pyruvoyl-tetrahydropterin synthase (PTPS) 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. PTPS deficiency should be suspected in all infants with a positive neonatal screening test for phenylketonuria, especially when hyperphenylalaninemia is moderate. The most effective way to diagnose the disorder is to measure pteridine levels in urine and to confirm the result by measuring neurotransmitters 5-hydroxyindolacetic acid (5-HIAA) and homovanillic acid (HVA) in cerebrospinal fluid and with by an oral tetrahydrobiopterin-loading test (20 mg/kg). When left untreated, the deficiency causes neurological signs at age 4 or 5 months, although clinical signs are often obvious from birth. The principal symptoms include psychomotor retardation, tonus disorders, convulsions, drowsiness, irritability, abnormal movements, hyperthermia, hypersalivation and difficulty swallowing. Treatment attempts to bring phenylalaninemia levels back to normal (diet with restricted phenylalanine intake or prescription of tetrahydrobiopterin) and to restore normal monoaminergic neurotransmission by administering precursors (L-dopa/carbidopa and 5-hydroxytryptophan).

Keywords
malignant hyperphenylalaninemia, tetrahydropterin deficiency, defective monoaminonergic neurotransmission, restricted phenylalamine intake.

Disease name and synonyms

6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency;
Biopterin-synthetase deficiency;
Tetrahydrobiopterin deficiency;
Malignant hyperphenylalaninemia.

Excluded diseases

Other hyperphenylalaninemias (phenylketonuria (PKU), mild hyperphenylalaninemia, etc.); other tetrahydrobiopterin deficiencies (GTP-

cyclohydrolase (GTPch) deficiency, dihydropteridin reductase (DHPR), pterin-4α-carbinolamine dehydratase (PCD).

Diagnostic criteria/definition

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

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 confident prediction of good outcome with a low phenylalanine diet can be made.
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

PTPS deficiency is the most frequent condition resulting from tetrahydrobiopterin deficiency: 196 cases are known (58% of which are tetrahydrobiopterin-deficient patients) (in France : 17 cases).
Consanguinity exists in 1/3 of the cases.
In countries where the incidence of PKU is low (Japan, Taiwan, etc.), the relative frequency (mainly PTPS deficiency) may appear high.

Clinical description

Typical forms

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, decreased spontaneous movements, floppy baby) can be observed.
The main 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. Convulsions (grand mal or myoclonic attacks) are frequently reported.
Considering growth parameters, most PTPS-deficient patients showed mild to severe failure to thrive. Microcephaly (head circumference < mean minus standard deviations for age) is observed in half of the cases.
The neuroradiological and electrophysiological abnormalities are 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 69% of PTPS-deficient patients, paroxysmal activity (hypsarrhythmia, sharp waves, epileptic discharges) was observed in 17% of the patients. Neuroanatomical investigations (CT scan & MRI) showed frequent and rather early brain atrophy.

Atypical forms

The absence of clinical signs is one of the criteria applied to classify patients in this group. However, clinical abnormalities have been noted in some of them.
The report of normal cerebrospinal fluid (CSF) neurotransmitter and biopterin levels led to the introduction of the term,"peripheral" form of PTPS deficiency.

Management including treatment

Typical forms

The goal is to control hyperphenylalaninemia by dietary restriction of phenylalanine or tetrahydrobiopterin administration, and to restore neurotransmitter homeostasis by oral administration of amine precursors L-dopa and 5-hydroxy-tryptophane (5HT). Carbidopa, an inhibitor of peripheral aromatic amino-acid decarboxylase, enables reduction of the therapeutic dose of L-dopa.
The doses usually given are L-dopa/carbidopa : 5-10 mg/kg body weight (bw)/day 5HT : 5-10 mg/kg bw/ day. However, doses can vary, and indeed have to be adapted to each individual. Neurotransmitter doses are usually divided into three equal portions during the day. 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 the possible disappearance of neurological symptoms when they exist. Unfortunately, there are no biochemical parameters measurable in the periphery (except hyperprolactinemia which is a good indicator of the hypothalamic dopamine deficiency) adequately monitor treatment; consequently, analyzing neurotransmitter metabolites in CSF, obtained by lumbar puncture, represents the most direct way to evaluate its efficacy, at least from a biochemical point of view.
Although tetrahydrobiopterin-deficient subjects exhibit higher dietary phenylalanine tolerance than classical PKU patients, a factor limiting 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. The use of tetrahydrobiopterin to control blood phenylalanine levels appears to be effective and is recommended. Relatively low doses of tetrahydrobiopterin (5-10 mg/kg/d) normalize blood phenylalanine levels and offer an alternative to a phenylalanine-restricted diet.

Atypical forms

These forms theoretically do not require a treatment, and thus the decision to treat or not is not evident. With regard to the obvious heterogeneity and the unclear prognosis, it seems appropriate to treat newborns with the so-called "peripheral" form at least with tetrahydrobiopterin, to monitor their development carefully and to reevaluate the metabolic status at 6 months of age.

Diagnostic methods

The diagnosis has to be considered for all conditions with hyperphenylalaninemia. PTPS deficiency can be surmised from measurements of related metabolites in urine, blood and CSF.

Typical forms

Urine pterin patterns are characteristic in PTPS deficiency. They not only show low or undedectable biopterin (B) levels but also markedly elevated neopterin (N), a pterin derived from the normal precursor of biopterin (7,8-dihydroneopterin-triphosphate). As a result, the N/B ratio is high, and the %B (B/B+N) is low. In CSF, the pterin pattern is similar. However, in some patients 2-3 weeks, biopterin values were within the normal range but the N/B ratio elevated.

In CSF, 5-HIAA and HVA levels are low. However, during the neonatal period, results can be within the normal ranges.

The tetrahydrobiopterin-loading test (2-20 mg/kg), by supplying the missing cofactor of phenylalanine hydroxylase (PAH), gives a prompt fall in plasma phenylalanine levels, as observed in all the patients subjected to the test. Because DHPR is intact, tetrahydrobiopterin functions catalytically and small amounts of cofactor hydrolyze large amounts of phenylalanine (even with a preload phenylalanine concentration as high as 40 mg/dl).

Erythrocytes were found to have PTPS activity, thus simplifying the investigation of patients. Most typical patients had very low PTPS activities.

Atypical forms

Determination of plasma and urine pterin levels alone will not distinguish these patients from those with typical PTPS deficiency but, in some cases, biopterin excretion was at the lower limit of the normal range. In such a situation, developmental changes, infectious disease or renal failure must be taken in account.

In contrast, CSF pterins usually contain higher biopterin levels, which are, in some patients, at the upper limit of the normal range. Nevertheless, a high N/B ratio confirms the existence of impaired tetrahydrobiopterin metabolism.

Neurotransmitter levels in CSF are usually reported to be normal. However, a decrease of CSF 5-HIAA levels exceeding that expected because of increasing age, has been observed. These observations suggest that patients exhibiting such a phenotype during the first months of life should be reevaluated after infancy.

Genetic counseling

PTPS deficiency is a genetic disorder with autosomal recessive inheritance, the disease occurs in both sexes and consanguinity is common. The gene *(PTS)* has been located on chromosome 11q22.3-q23.3 (6 exons), 33 mutations have been described.

Antenatal diagnosis

The option of prenatal diagnosis is likely to be taken seriously, since these conditions are subject to much uncertainty about the prognosis. It is possible to diagnose PTPS deficiency prenatally by measuring of pterin levels in amniotic fluid and PTPS in fetal erythrocytes. DNA analysis can also be used.

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