Defect in GTP-cyclohydrolase

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Abstract
GTP-cyclohydrolase I 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. GTP-cyclohydrolase I 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, homovanillic acid) in cerebrospinal fluid and with 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, tonicity disorders, convulsions, drowsiness, irritability, abnormal movements, hyperthermia, hypersalivation, and difficulty swallowing. The 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-hydroxytryptophane).

Keywords
Tetrahydrobiopterin deficiency, malignant hyperphenylalaninemia autosomal recessive transmission, defective neurotransmisssision.

Disease name and synonyms

- GTP-cyclohydrolase deficiency (GTPch, EC.3.5.4.16);
- Tetrahydrobiopterin deficiency ;

malignant hyperphenylalaninemia.

Excluded diseases

Other hyperphenylalaninemias (phenylketonuria (PKU), mild hyperphenylalaninemia); other tetrahydrobiopterin deficiencies (Dihydropteridine reductase (DHPR) deficiency,

6-pyruvoyl-tetrahydropterin synthase (PTPS), pterin-4 alpha-carbinolamine dehydratase (PCD); dopa-responsive dystonia (DRD).

Diagnostic criteria/definition

GTPch deficiency is one of the etiologies of "malignant hyperphenylalaninemia" which result from tetrahydrobiopterin deficiency. In addition to being hyperphenylalaninemic, patients lacking tetrahydrobiopterin are deficient in the neurotransmitters whose synthesis depend on the normal activity of tetrahydrobiopterin-dependent tyrosine and tryptophan hydroxylases (EC.1.14.16.2 and EC.1.1

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 good disease control with a low-phenylalanine diet can be predicted with confidence.

It is recommended that all infants with hyperphenylalaninemia should 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

GTPch deficiency is a rare condition: 16 cases are known (5% of whom are tetrahydrobiopterin-deficient patients) and they derive from 13 families (in France: 4 cases in 2 families). Consanguinity exists in 1/3 of the cases.

Clinical description

The median age at which clinical signs become evident is 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 tonus and posture, drowsiness, irritability, abnormal movements, recurrent hyperthermia without infection, hypersalivation, swallowing difficulties. Diurnal fluctuation of alertness and neurological symptoms are often reported.

The neuroradiological and electrophysiological abnormalities are often less severe than would be expected from the clinical picture.

Management including treatment

The aim 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-hydroxytryptophan (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 of 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, no biochemical parameters measurable in the periphery (except hyperprolactinemia which is a good indicator of the hypothalamic dopamine deficiency) adequately monitor the treatment. Consequently, analyzing neurotransmitter metabolites in cerebrospinal fluid (CSF) obtained by lumbar puncture represents the most direct way to evaluate treatment's efficiency, 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 hydroxylase.

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/day) normalize blood phenylalanine levels and offer a possible alternative to a phenylalanine-restricted diet.

Diagnostic methods

The diagnosis has to be considered in all conditions with hyperphenylalaninemia.

Biopterin and neopterin levels are dramatically decreased in all biological fluids, but are still measurable (up to 10% of normal). The origin of these non-negligible amounts of pterins is still a subject for speculation (residual activity of mutated GTPch, nutrition or intestinal flora).

Neurotransmitters, 5-hydroxyindolacetic acid (5-HIAA) and homovanillic acid, (HVA) in CSF are low.

The tetrahydrobiopterin-loading test (20 mg/kg), by supplying the missing cofactor of phenylalanine hydroxylase (PAH), causes a prompt fall in plasma phenylalanine levels

GTPch activity is measurable in liver and phytohemagglutinin-stimulated blood lymphocytes.

Genetic counseling

GTPch deficiency is a genetic disorder with autosomal recessive inheritance; it occurs in both sexes and consanguinity is common. The gene (GCH1) has been located on chromosome 14q21-q22 (6 exons); 20 mutations have been reported since 1997.

Antenatal diagnosis

The option of prenatal diagnosis is likely to be taken seriously, since the prognosis of these conditions are much uncertain.

Since GTPch is not expressed in chorionic villi, amniocytes or fetal erythrocytes, the antenatal diagnosis of GTPch deficiency is restricted to the analysis of amniotic fluid pterins. However, difficulties in differentiating between homozygous and heterozygous carriers of the defect theoretically exist and the contribution of maternal pterins through the placenta is unknown.

DNA analysis can solve these problems.

References

Blau N., Barnes I., Dhondt J.L. International Database of Tetrahydrobiopterin Deficiencies. J Inherit Metab Dis 1996, 19: 8-14

Dhondt J.L. Strategy for the screening of tetrahydrobiopterin deficiency among hyperphenylalaninemic patients: 15 years experience. J. Inherit. Metab. Dis. 1991, 14, 117-127

Dhondt J.L. Tetrahydrobiopterin deficiencies. Lessons from the compilation of 200 patients. Developmental Brain Dysfunction 1993, 6, 139-155

Dhondt J.L., Tilmont P., Ringel J., Farriaux J.P. Pterin analysis in amniotic fluid for the prenatal diagnosis of GTP cyclohydrolase deficiency. J. Inherit. Metab. Dis. 1990, 13, 879-882

International register of tetrahydrobiopterin deficiencies (J.L. Dhondt, N. Blau): http://www.bh4.org/ (BIODEF (patients database) and BIOMDB (mutations database).

Niederwieser A., Staudenmann W., Wang M., Curtius H.C, Atares M., Cardesa-Garcia J. Hyperphenylalaninemia with neopterin deficiency, a new enzyme defect presumably of GTP cyclohydrolase. Eur. J. Pediatr. 1982, 138, 97

Scriver CR, Kaufman S, Eisensmith RC, Woo SLC. The hyperphenylalaninemias. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular Bases of Inherited Disease, 7th edn, vol. 1. New York: McGraw-Hill, 1995, 1015-1075