Abnormalities of tetrahydrobiopterin metabolism

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Introduction

This article includes discussion of abnormalities of tetrahydrobiopterin metabolism, BH₄ deficiency, dihydropteridine reductase deficiency, GTP cyclohydrolase deficiency, pterin-4 alpha-carbinolamine dehydratase deficiency, sepiapterin reductase deficiency. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

Tetrahydrobiopterin (BH₄) deficiencies, a group of rare inherited neurologic diseases with monoamine neurotransmitter deficiency, may present with or without hyperphenylalaninemia (HPA). Tetrahydrobiopterin (BH₄) is an essential cofactor not only for phenylalanine hydroxylase, but also for tyrosine and 2 tryptophan hydroxylases, 3 nitric oxide synthases, and glyceryl-ether monooxygenase. Defects of BH₄ metabolism comprise a group of treatable pediatric neurotransmitter disorders. The major pathophysiology consists of disturbed phenylalanine homeostasis, as well as compromised catecholamine and serotonin biosynthesis. This heterogeneous group of disorders is caused by mutations in either 6-pyruvoyl-tetrahydropterin synthase, GTP cyclohydrolase, pterin-4 alpha-carbinolamine dehydratase deficiency, sepiapterin reductase, or dihydropteridine reductase. Affected patients are usually clinically asymptomatic at birth and in early infancy. Without diagnosis and treatment they develop a progressive encephalopathy characterized by severe truncal hypotonia, decreased spontaneous movements, movement disorders, including chorea and dystonia, intellectual disability, and epileptic seizures. BH₄ is also involved in cardiovascular and endothelial dysfunction and pain modulation.

Many patients present with hyperphenylalaninemia, which may be detected through newborn phenylketonuria screening programs. Two forms of cerebral BH₄ deficiency may occur without hyperphenylalaninemia: the autosomal dominantly inherited form of GTPCH deficiency (dopa-responsive dystonia, initially described as Segawa disease, see also the chapter Dopa-responsive dystonia) and the recently delineated sepiapterin reductase deficiency. Treatment of tetrahydrobiopterin deficiencies relies on the use of a mixture of levodopa and carbidopa (ie, Sinemet®), 5-hydroxytryptophan, tetrahydrobiopterin and, if necessary, a low-phenylalanine diet and an additional supplementation of folinic acid in the treatment of dihydropteridine reductase deficiency. Treatment should be initiated as early as possible and continued for life.

Key points

- Tetrahydrobiopterin (BH₄) deficiencies affect phenylalanine homeostasis, but most importantly impair catecholamine and serotonin biosynthesis.
- Five enzyme defects are all inherited in an autosomal recessive manner.
- Without early diagnosis and treatment, BH₄ deficiencies result in progressive developmental impairment and severe neurologic dysfunction.
- Any baby presenting with any degree of hyperphenylalaninemia in the newborn screening program must be evaluated in a timely manner to exclude or diagnose 1 of the BH₄ deficiencies.

Historical note and terminology

Phenylketonuria comprises a group of conditions that arise as a result of the inability to effectively convert phenylalanine to tyrosine. The first case was reported by Folling in 1934, and subsequent studies demonstrated that the majority of cases were due to defects of phenylalanine hydroxylase. Dietary control of the disease using a phenylalanine-restricted diet was introduced in 1953 by Horst Bickel and colleagues. In 1974, there were 2
independent reports of children with a form of phenylketonuria that was accompanied by a complex severe progressive neurologic illness unresponsive to dietary treatment (Bartholome 1974; Smith 1974). It was already hypothesized that these children lacked tetrahydrobiopterin, the cofactor required for the phenylalanine hydroxylase reaction. Tetrahydrobiopterin is formed from GTP in a multistep pathway involving dihydروytrinetrin and tetrahydropterin intermediates. During the hydroxylation of phenylalanine, tetrahydrobiopterin is oxidized to quinonoid dihydrobiopterin by pterin-4 alpha-carbinolamine dehydratase, and then reduced back to tetrahydrobiopterin by the action of dihydropteridine reductase (Werner et al 2011).

In addition to the phenylalanine hydroxylase reaction, tetrahydrobiopterin is also the cofactor for tyrosine hydroxylase and tryptophan hydroxylase, the rate-limiting enzymes required for the synthesis of the catecholamines and serotonin, the generation of nitric oxide from citrulline by nitric oxide synthases, and the production of an alkyl aldehyde and glycerol from a glycerol ether by glyceryl-ether monooxygenase (Werner et al 2011). The continuing deficiency of these neurotransmitters within the central nervous system explains why the neurologic symptoms in children with defects in tetrahydrobiopterin metabolism do not respond clinically to a low-phenylalanine diet alone.

Proof of a problem in cofactor metabolism came following demonstration of dihydropteridine reductase (DHPR) deficiency in the brain and liver of another child with phenylketonuria whose neurologic symptoms were unresponsive to diet (Kaufman et al 1975). In 1976 evidence appeared for a defect affecting the biosynthesis of tetrahydrobiopterin (Leeming et al 1976). In this case, low concentrations of biopterins were found and an unusual pterin was detected (later identified as neopterin). Identification of low concentrations of biopterins in association with high concentrations of neopterins indicated a block after the formation of dihydروytrinetrin triphosphate. Additional reports soon confirmed that this new entity was due to a defect in the synthesis of tetrahydrobiopterin. At that time, the biosynthetic pathway for tetrahydrobiopterin was thought to occur via a dihydrobiopterin intermediate, and the new defects were classified as “dihydrobiopterin synthetase deficiencies.” It is now known that tetrahydrobiopterin is synthesized via tetrahydropterin intermediates and the enzyme deficiency leads to blockage at the level of 6-pyruvoyltetrahydropterin synthase (PTPS). Previous names for this enzyme have included dihydrobiopterin synthetase, phosphate eliminating enzyme and sepiapterin synthesizing enzyme-1. More than half of the patients with BH4 deficiencies suffer from a deficiency of this enzyme (Opladen et al 2012).

In 1984 a defect affecting GTP cyclohydrolase 1, the first enzyme in the biosynthetic pathway for tetrahydrobiopterin synthesis, was described (Niederwieser et al 1984). Since then several other cases have been reported (Blau et al 2001; Opladen et al 2012). Not all cases of autosomal recessively inherited GTP cyclohydrolase deficiency have hyperphenylalaninemia; however, severe neurotransmitter deficiencies are detectable in CSF analyses. In several reported cases with well-defined, confirmed pathogenic mutations, progressive severe neurologic symptoms developed which responded well to L-Dopa supplementation. These included neonatal-onset of rigidity, tremor, spasticity, oculogyric crises, and dystonia (Furukawa et al 1998; Horvath et al 2008; Opladen et al 2011). Abnormal phenylalanine metabolism could only be demonstrated after stressing the phenylalanine to tyrosine hydroxylation system by administering a phenylalanine loading challenge. The clinical spectrum of GTP cyclohydrolase 1 deficiency includes the classical dominant L-Dopa-responsive dystonia without hyperphenylalaninemia, type Segawa, at the mildest, to neonatal onset of progressive spasticity, rigidity, tremor, dystonia, and hyperphenylalaninemia in autosomal recessive dopa-responsive dystonia at the other end of the continuum. Intermediate phenotypes with graded clinical symptoms can be related to compound heterozygous mutations resulting in different residual activities, again sometimes without overt hyperphenylalaninemia.

In 1988, a new type of defect affecting tetrahydrobiopterin metabolism was found (Dhondt et al 1988). Dhondt and colleagues observed an unusual peak by HPLC used to screen for defects in tetrahydrobiopterin metabolism. This compound was later identified as 7-substituted biopterin (as opposed to the normal 6-substituted biopterin). It was shown to result from a deficiency of pterin-4 alpha-carbinolamine dehydratase, which functions as part of the phenylalanine hydroxylating system in the conversion of 4a-OH-tetrahydrobiopterin to quinonoid dihydrobiopterin.

In 1994, dopa-responsive dystonia was shown to be associated with dominant mutations in the gene for GTP cyclohydrolase 1 (Ichinose et al 1994). This disorder was first described by Segawa, who named the disorder “hereditary progressive dystonia with marked diurnal fluctuation” (Segawa 1976). Unlike the other defects in tetrahydrobiopterin metabolism, this condition is inherited in an autosomal dominant fashion, and affected and asymptomatic carriers of the mutation do not have hyperphenylalaninemia under resting conditions (Hyland et al 1997; Opladen et al 2010).
In 1998, another defect in tetrahydrobiopterin metabolism was described that did not lead to hyperphenylalaninemia. It was first presumed to be a variant of dihydropteridine reductase deficiency (Blau et al 1999) but was later shown to be due to sepiapterin reductase deficiency (Bonafe et al 2001b). Central nervous system catecholamine and serotonin metabolism were impaired leading to severe neurologic dysfunction.

Terminology for the group of defects that affect tetrahydrobiopterin metabolism has altered since the early descriptions. Initial cases were classified as forms of atypical phenylketonuria and then malignant hyperphenylalaninemia because they were unresponsive to classic dietary treatment. Currently, the term "tetrahydrobiopterin deficiencies" encompasses all of the disorders.

The BH₄ deficiencies are clinically heterogeneous. There are variant forms of 6-pyruvoyltetrahydropterin synthase deficiency (transient cases, peripheral forms, and severe forms that affect both systemic and central systems) as well as several partial and mild cases of dihydropteridine reductase deficiency (Blau et al 1992; Opladen et al 2012).

Several different names have also been used to describe the autosomal dominantly inherited form of GTP cyclohydrolase 1. The condition was initially termed "hereditary progressive dystonia with marked diurnal fluctuation" or more commonly "Segawa syndrome." Since 1988, the term "dopa-responsive dystonia" has generally been applied to all dystonias responding to levodopa (Nygaard 1988), which includes autosomal dominant dopa-responsive dystonia caused by mutations in the GTP cyclohydrolase 1 gene (Ichinose et al 1994) (see also the article Dopa-responsive dystonia).

More than 600 individuals with recessively inherited defects affecting tetrahydrobiopterin metabolism have been reported (Opladen et al 2012). Of these, 355 patients, 56.7% had PTPS deficiency; 217 patients, 34.7%, had DHPR deficiency; 31 patients, 4.9%, had GTP cyclohydrolase deficiency; 23 patients, 3.7%, had pterin-4 alpha-carbinolamine dehydratase deficiency; and 43 patients, 6.8%, had sepiapterin reductase deficiency (Friedman et al 2012). The number of described cases of the autosomal dominantly inherited GTP cyclohydrolase 1 deficiency has increased rapidly since the molecular lesion was described (Ichinose et al 1994). A web site listing all details regarding the defects of tetrahydrobiopterin metabolism is updated regularly and can be accessed at the Tetrahydrobiopterin Home Page.

**Clinical manifestations**

**Presentation and course**

The presenting clinical signs of untreated autosomal recessively inherited GTP cyclohydrolase deficiency of untreated severe forms of 6-pyruvoyltetrahydropterin synthase deficiency and of dihydropteridine reductase deficiency are similar and are due in most part to the reduced synthesis of the biogenic amine neurotransmitters. In the neonatal period, there may be poor sucking, decreased spontaneous movements, floppiness, and microcephaly (Blau et al 2001; Opladen et al 2012). The increased incidence of decreased birth weight in 6-pyruvoyltetrahydropterin synthase deficiency and the appearance of neurologic signs at an earlier age in this disease as compared to dihydropteridine reductase deficiency have been attributed to effects in utero (Smith and Dhondt 1985).

Obvious neurologic signs appearing after 2 months of age include truncal hypotonia, pinpoint pupils, and brisk tendon reflexes, as well as movement disorders such as hypokinesia, distal chorea, myoclonus, and oculogyric crises. Developmental retardation is commonly observed. Less frequent symptoms comprise muscular hypertonia and convulsions (grand mal or myoclonic), the latter being more frequent in dihydropteridine reductase deficiency. Autonomic symptoms, hypersalivation, temperature disturbance (in the absence of infection), sweating, swallowing difficulties, drowsiness, and irritability can be very troublesome (Blau et al 2001; Opladen et al 2012). Diurnal fluctuation of symptoms is frequently observed, most likely due to the effects of the concurrent fluctuation of monoamines. If not diagnosed there may be progressive neurologic deterioration and microcephaly.

EEG findings are abnormal in approximately 90% of dihydropteridine reductase-deficient patients and 80% of 6-pyruvolyt-tetrahydropterin synthase-deficient patients (n=24). EEG patterns were nonspecific and did not allow differentiation between the individual BH₄ deficiencies (Opladen et al 2012).

An insidious deficiency of folate may occur in dihydropteridine reductase deficiency (Kaufman et al 1975; Smith et al 1985). This is usually not associated with megaloblastic changes and if not recognized can lead to devastating changes within the central nervous system. Brain lesions consist of multifocal, perivascular demyelination in the

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subcortical white matter accompanied by perivascular microcalcification, which is also present in the basal ganglia (Smith et al 1985).

Variant forms of 6-pyruvoyltetrahydropterin synthase and dihydropteridine reductase deficiency have been described in which the neurologic signs are either minor or absent. A late onset case of 6-pyruvoyltetrahydropterin synthase deficiency was described where dystonia was the major symptom at the age of 44 years (Hanihara et al 1997). Two cases with dihydropteridine reductase deficiency have been studied in detail (Blau et al 1992). In these there was some residual activity of the enzyme in fibroblasts. In 1 untreated child, plasma phenylalanine ranged from 73 to 399 mmol/L, and there were no neurologic signs at 18 months. In the second case, treatment with 10 mg/kg of tetrahydrobiopterin per day was commenced after 3 months because of reduced concentration of 5-hydroxyindoleacetic acid in CSF. Psychomotor development was normal until 30 months, at which time a deceleration of head growth was observed. In both of these cases, concentrations of homovanillic acid in CSF were always normal, whereas concentrations of 5-hydroxyindoleacetic acid were greatly reduced.

Some children with recessively inherited GTP cyclohydrolase deficiency also did not have hyperphenylalaninemia (Furukawa et al 1998; Horvath et al 2008; Opladen et al 2011). The severity of clinical presentations was different. Female twins presented with neonatal onset of rigidity, tremor, and dystonia suggestive of a diffuse CNS involvement; a female presented with typical features of tetrahydrobiopterin deficiency at around 6 months of age, whereas a male presented with a clinical picture more like that seen in the autosomal dominantly inherited GTP cyclohydrolase deficiency. Between the ages of 4 and 6 years, he lost motor and speech function, developed generalized dystonia, and symmetrical hyperreflexia with bilateral extensor plantar responses. Oral phenylalanine loading in these patients showed a decreased ability to convert phenylalanine to tyrosine, demonstrating a compromised phenylalanine hydroxylation system in the liver (Furukawa et al 1998; Horvath et al 2008; Opladen et al 2011).

In 1999, two children were described who had the typical clinical course and neurochemical profile of dihydropteridine reductase deficiency. However, hyperphenylalaninemia was not present, suggesting a form of the disease that is localized to the central nervous system (Blau et al 1999); these children were later shown to have sepiapterin reductase deficiency (Bonafe et al 2001b). Hyperphenylalaninemia is absent in these patients because 3-alpha-hydroxysteroid dehydrogenase and aldose reductase replace the activity of sepiapterin reductase in the liver (Hirakawa et al 2009). These enzymes are not present in the brain.

More than 50 cases of sepiapterin reductase deficiency have been described (Friedman et al 2012). Almost all patients exhibited hypotonia in the first few months of life. Subsequent symptoms included progressive dystonia, chorea, oculogyric crises, tremor, spasticity, microcephaly, growth retardation, depressive and aggressive behavior, and psychomotor retardation. Diurnal variation is usually present. Signs of autonomic dysfunction have included hypersalivation, temperature instability, lethargy, hypersomnolence, and episodes of sweating and pallor. Initially, patients are often misdiagnosed as having cerebral palsy, and delay in determining the correct diagnosis can be many years or even decades. Although most patients present with a typical dopa-responsive dystonia, dystonia may be absent.

None of the prominent signs of abnormal serotonin and catecholamine metabolism are typically found in either pterin-4-alpha-carbinolamine dehydratase deficiency, or the atypical forms of 6-pyruvoyltetrahydropterin synthase deficiency, and the concentrations of homovanillic acid and 5-hydroxyindoleacetic acid in CSF are essentially normal. More than 75% of neonates with the mild phenotype of 6-pyruvoyltetrahydropterin synthase deficiency (ie, initially normal neurotransmitters in the CSF, treated with BH4 monotherapy, approximately 20% of all patients) are asymptomatic throughout life. However, 15% of those develop with retardation, dystonia, movement disorders, or autonomic symptoms. Some will also develop very low concentrations of neurotransmitter metabolites after several months. Minor neurologic signs consisting of slight tremors of upper limbs and hypertonia or hypotonia have been reported in the neonatal period in pterin-4-alpha-carbinolamine dehydratase deficiency. Only 1 of 23 patients listed in the BIODEF database needed a substitution with BH4 and neurotransmitter precursors. However, several patients were found to develop neurologic abnormalities and developed maturity-onset diabetes of the young (MODY) type 3 and insulin resistance in adolescence (Simaite et al 2014). It has been suggested that all patients with disorders of biopterin metabolism should be regularly reevaluated in terms of their central amine status and continued to be followed in a specialized center.

The autosomal dominantly inherited form of GTP cyclohydrolase deficiency (dopa-responsive dystonia) classically presents as a dystonic gait disorder with diurnal variation of symptoms. The mean age of onset of symptoms is 5 years
to 6 years. The first symptom is usually postural dystonia of 1 leg, with progression to all limbs, followed by action dystonia and hand tremor within the next 10 to 15 years, during which time cognition remains intact. Occasionally, in older children, the first signs may start in the arms or be torticollis or writer's cramp (focal dystonia). The spectrum of clinical manifestations is, however, broad and may include a total absence of symptoms, minor muscle cramps, infantile or adult onset, an early nonprogressive course, delayed attainment of motor milestones, spastic diplegia, and the occurrence of parkinsonian-like features in later life (Nygaard 1993). A patient has also been described in whom the first symptom was an adult-onset oromandibular dystonia (Steinberger et al 1999); in others, presentation was an apparent primary torsion dystonia that was responsive to anticholinergic agents (Jarman et al 1997) or with a myoclonus-dystonia syndrome (Leuzzi et al 2002). Penetrance is reduced, with the frequency of symptoms being 3-fold to 4-fold higher in females, as compared to males (Nygaard 1993).

Of those patients who present at the mean age with the typical dystonic gait disorder, 20% also have hyperreflexia and apparent extensor plantar responses, as well as other clinical features suggesting spasticity. These together with the prominent upper motor neuron findings, including spastic diplegia, which has in many cases led to a diagnosis of cerebral palsy.

The GTP cyclohydrolase gene also has been suggested as a susceptibility gene in bipolar disorder (Kealey et al 2005), and a tetrahydrobiopterin deficit has been demonstrated in schizophrenia although the cause of the deficit is unclear (Richardson et al 2005).

**Prognosis and complications**

The response to treatment and the prognosis following treatment depends on the age at which treatment is begun and the degree of damage that has already occurred prior to the initiation of therapy (Opladen et al 2012). The prognosis for untreated patients with the typical recessively inherited forms (those requiring treatment of a central serotonin and catecholamine deficiency) of tetrahydrobiopterin deficiency is poor, with many patients dying within the first few years of life. When treatment begins in the neonatal period, patients are frequently asymptomatic or show less retardation, movement disorders, and convulsions. Some degree of neurologic improvement is generally seen in all children, even if treatment is started late. However, in individual cases the overall outcome is quite variable. In some cases, outcome is poor, despite normalization of plasma phenylalanine and correction of the central amine deficiency within a few weeks of birth. In other cases, near normal developmental progress is achieved. Patients with dihydropteridined reductase deficiency may initially make good progress following correction of plasma phenylalanine, and the central neurotransmitter deficiency only to succumb to a devastating neurologic degeneration as a result of the central folate deficiency that can arise as a secondary manifestation of this disease (Smith et al 1985; Dhondt 1991).

Prognosis for patients with the autosomal dominantly inherited GTP cyclohydrolase deficiency (dopa-responsive dystonia) is good once the diagnosis has been made and treatment with levodopa has commenced. In most cases complete recovery is achieved, cognitive function does not seem to be impaired, and no adverse effects of the levodopa therapy have been reported once the correct dosage has been ascertained.

**Clinical vignette**

The male patient from first-cousin parents of Turkish ancestry was born after transitory neonatal distress secondary to maternal infection. Postpartum recurrent hypoglycemia (on admission 22 mg/dL), dyspnea, and metabolic acidosis quickly resolved. The development was considered normal, until a first prolonged afebrile seizure occurred when he was 6 months old. EEG showed generalized hypersynchronous activity. In the next month he developed recurrent generalized clonus with dystonic movements of the left hand and arm, episodic recurrent deviation of the eyes to the left and the right upper side, as well as varying opisthotonic posturing. This combination of symptoms was interpreted as seizures and antiepileptic therapy was started with phenobarbital. This led to an amelioration of symptoms, but the eye deviations persisted. In retrospect, these typical oculogyric crises were interpreted as atypical absences (EEGs and cranial MRI at the age of 12 months were normal). The neurologic status slowly worsened and the boy developed generalized spasticity and pyramidal signs. Progressive global developmental delay became more and more obvious. At the age of 18 months phenobarbital was stopped and he was recognized as having dystonia and ataxic posturing for the first time, in addition to tetraspasticity.

At the age of 7 years, he was reevaluated. It was recognized that his motor functions worsened during the day and from day to day. He could walk in the morning although with a dystonic gait and spasticity. Later in the day, he had to
use a wheelchair. He had a cogwheel muscular resistance and for the first time the eye deviations were correctly interpreted as oculogyric crises. A lumbar puncture for the analysis of neurotransmitter metabolites was performed confirming neurotransmitter disease, specifically dopamine and serotonin deficiency, which was finally delineated to be due to sepiapterin reductase deficiency. Therapy with L-Dopa without carbidopa was started with 4 mg/kg bw/d and slowly increased up to 16 mg/kg bw/d. The child learned to walk and run, to go up- and downstairs without holding on to a banister, and finally, to play soccer and dance. He is now 22-years-old and almost walking normally. His handwriting is nearly normal (initially he could not write at all). He is able to speak normal sentences in German and Turkish, which became more clearly and distinctly pronounced from year to year. He has become more self-confident, finished schooling for physically handicapped people, and started working. Intellectual function remained below average.

**Biological basis**

**Etiology and pathogenesis**

Tetrahydrobiopterin (BH₄) is an essential cofactor for phenylalanine, tyrosine, and tryptophan hydroxylases (the last 2 being the rate-limiting enzymes in catecholamine and serotonin biosynthesis, respectively). In addition, BH₄ is an essential cofactor for the 3 isoforms of nitric oxide synthase. It is also involved in cardiovascular and endothelial dysfunction, and pain modulation. The de novo pathway for the biosynthesis of BH₄ from GTP requires 3 enzymes, GTP cyclohydrolase (committing and rate-limiting step), 6-pyruvoyltetrahydropterin synthase, and sepiapterin reductase. Regeneration of BH₄ is an essential part of the system. BH₄ is hydroxylated and oxidized to form tetrahydrobiopterin-4 alpha-carbinolamine, which produces q-dihydrobiopterin after the removal of a water molecule by pterin-4 alpha-carbinolamine dehydratase. In the final step, dihydropteridine reductase regenerates BH₄ from q-dihydrobiopterin.

The deficiencies of GTP cyclohydrolase, 6-pyruvoyltetrahydropterin synthase, sepiapterin reductase, dihydropteridine reductase, and pterin-4 alpha-carbinolamine dehydratase are autosomal recessive disorders, the exception being the autosomal dominantly inherited form of GTP cyclohydrolase deficiency (dopa-responsive dystonia). All defects have been molecularly characterized (Thony and Blau 2006). Mutations in dihydropteridine reductase deficiency are a variety of mutations throughout the coding region, with a corresponding variation of effects on the structure and function of the protein. In addition, mutations leading to 2 cases of a mild atypical form of dihydropteridine reductase deficiency have been located (Blau et al 1992). So far, the study of these mutations has not revealed the tetrahydrobiopterin binding domain.

A study of the mutations in 6-pyruvoyltetrahydropterin synthase deficiency demonstrated that a typical form of the disease is due to a homozygous G-to-A transition at codon 25, causing a replacement of arginine by glutamine. A peripheral defect was caused by compound heterozygosity, 1 allele having a C-to-T transition resulting in substitution of arginine 16 for cysteine. On the second allele there was a 14-bp deletion leading to a frameshift at lysine 120 and a premature stop codon. Forty-two percent of Chinese patients with 6-pyruvoyltetrahydropterin synthase deficiency have a C259T missense mutation, which results in an amino acid change from proline to serine at codon 87. Many more mutations have been described. Of particular interest is that found in a patient with a homozygous missense mutation (K129E) who had transient hyperphenylalaninemia, but did not require tetrahydrobiopterin or neurotransmitter precursor therapy. No 6-pyruvoyltetrahydropterin synthase activity was detectable in fibroblasts or red blood cells. However, the mutant enzyme was 2-fold to 3-fold more active than the wild type when transfected into COS-1 cells and a human hepatoma cell line implying that there are cell-specific expression regulators for this protein (Oppliger et al 1997).

Only a few mutations have been reported in the GTP cyclohydrolase 1 gene causing the autosomal recessively inherited form of hyperphenylalaninemia. Two compound heterozygotes have also been described who did not have hyperphenylalaninemia in infancy, yet had severe central nervous system signs (Furukawa et al 1998). Most of the other mutations, which are scattered over the entire coding region are observed in the heterozygous state with the wild-type allele, and are associated with the dominant dopa-responsive dystonia (Blau et al 2001). It is suggested that a difference in the ratio of mutant to wild-type GTP cyclohydrolase mRNA that depends on the locus of a mutation might explain the intrafamilial and interfamilial variation of phenotype seen in dominantly inherited GTP cyclohydrolase deficiency. However, the finding of phenotypic heterogeneity in monozygotic twins demonstrates that other factors are also likely involved (Grotzsch et al 2004).

In a cohort of patients with sepiapterin reductase deficiency, 16 different mutations were described (7 missense, 4
nonsense, 3 frame-shift, 1 splice-site, and 1 in promoter region), the intronic homozygous variant c.596-2A>G being the most common (Friedman et al 2012). There was no correlation between neurologic presentation and course or cognitive function with either specific mutations or CSF metabolite concentrations.

The autosomal recessively inherited abnormalities of tetrahydrobiopterin metabolism usually cause a disturbance in the hydroxylation of phenylalanine and consequently, lead to hyperphenylalaninemia and phenylketonuria. Tetrahydrobiopterin is also the cofactor for tryptophan hydroxylase and tyrosine hydroxylase, the rate-limiting enzymes in the synthesis of serotonin and the catecholamines. The major neurologic features seen in the typical forms of these disorders are due to decreased synthesis and turnover of these neurotransmitters. Hyperphenylalaninemia is not a feature in patients with the autosomal dominantly inherited GTP cyclohydrolase deficiency, sepiapterin reductase deficiency, or some compound heterozygotes with GTP cyclohydrolase deficiency. An abnormality in phenylalanine metabolism can be exposed if the phenylalanine hydroxylation system is stressed by administration of an oral phenylalanine load (Hyland et al 1997; Hyland et al 1999; Bonafe et al 2001b).

Tetrahydrobiopterin is also required for the activity of nitric oxide synthase (Werner et al 2011). Nitrite and nitrate concentrations (indicators of nitric oxide concentrations) are low in spinal fluid from patients with tetrahydrobiopterin deficiencies, but it is currently unclear if the disturbed nitric oxide metabolism contributes to the neurologic or other symptoms.

An insidious deficiency of folate in the brain may occur in dihydropteridine reductase deficiency (Kaufman et al 1975; Smith et al 1985). This is usually not associated with megaloblastic changes and, if not recognized, can lead to devastating changes within the central nervous system. Brain lesions consist of multifocal, perivascular demyelination in the subcortical white matter accompanied by perivascular microcalcification in the basal ganglia (Smith et al 1985). The folate deficiency is thought to arise as a result of competitive inhibition of dihydrofolate reductase and 5,10-methylenetetrahydrofolate reductase by the 7,8- and quinonoid dihydrobiopterins that accumulate due to the absence of dihydropteridine reductase activity (Smith et al 1985).

It is possible that tetrahydrobiopterin deficiency leads to in utero pathology, because low birth weight, clinical signs, and microcephaly are found in both 6-pyruvoyltetrahydropterin synthase deficiency and dihydropteridine reductase deficiency. The incidence of these changes is higher in 6-pyruvoyltetrahydropterin synthase deficiency; it is suggested that tetrahydrobiopterin concentrations in dihydropteridine reductase deficiency may be maintained in utero by folate enzymes that are able to regenerate the active cofactor.

Prenatal diagnosis for the defects of tetrahydrobiopterin can be performed either by the analysis of neopterin and biopterin in amniotic fluid or by direct assay for the enzyme in fetal erythrocytes or by DNA analysis where mutations are defined (Blau et al 2001).

**Epidemiology**

The total incidence of tetrahydrobiopterin deficiency in newborns with hyperphenylalaninemia is between 2% and 3%. In Caucasian populations it is lower (less than 1% of hyperphenylalaninemic infants); however, in some places, such as Turkey, Brazil, China, Saudi Arabia, and Sicily, the incidences are much higher.

**Prevention**

Defects in tetrahydrobiopterin metabolism are mainly inherited in an autosomal recessive fashion. Mating of heterozygotes with the same enzyme deficiency can give rise to an affected child, with each pregnancy having a 1 in 4 chance of producing an affected fetus. Although the tetrahydrobiopterin deficiencies are treatable, the long-term outcome is still uncertain; genetic counseling for a family with previously documented cases of the typical deficiencies of GTP cyclohydrolase, dihydropteridine reductase, sepiapterin reductase, and 6-pyruvoyltetrahydropterin synthase is, therefore, recommended. Prenatal diagnosis is available for all conditions, either by measurement of biopterin and neopterin in amniotic fluid, by direct enzyme analysis in fetal cells, or by DNA analysis where mutations are defined (Blau et al 2001).

**Differential diagnosis**

The detection of hyperphenylalaninemia (in the absence of changes in other large neutral amino acids) by newborn screening in most cases of autosomal recessively inherited tetrahydrobiopterin deficiency allows rapid detection that
must be followed by timely differentiation of this group of diseases from other metabolic conditions affecting phenylalanine hydroxylase activity. It is important to distinguish between the tetrahydrobiopterin deficiencies and deficiency of phenylalanine hydroxylase and also to identify the exact site of the lesion leading to tetrahydrobiopterin deficiency because the treatment is different in each of the conditions. This is accomplished by examination of the pattern of biopterins and neopterins in urine, and by mutation analysis or direct measurement of enzyme activities (Hyland and Howells 1988; Hyland 1993). Under resting conditions, patients with the autosomal dominantly inherited GTP cyclohydrolase deficiency (dopa-responsive dystonia) or sepiapterin reductase deficiency do not have hyperphenylalaninemia; neither do patients who are compound heterozygotes for GTP cyclohydrolase deficiency. In those, a defect in the phenylalanine hydroxylation system can, however, be exposed by administration of an oral phenylalanine load (Hyland et al 1997; Hyland et al 1999; Bonafe et al 2001b; Opladen et al 2010).

The neurologic symptoms found in typical autosomal recessively inherited cases of the tetrahydrobiopterin deficiencies in the neonatal period are nonspecific (they include poor sucking, decreased spontaneous movement, floppiness, and microcephaly) (Hyland 1993; Opladen et al 2012), and do not allow clinical diagnosis in a situation where newborn screening for hyperphenylalaninemia is not performed. More obvious neurologic signs appear after 2 months of age, and include hypersalivation and temperature disturbance (in the absence of infection), sweating, pinpoint pupils, oculogyric crises, hypokinesia, distal chorea, truncal hypotonia, swallowing difficulties, drowsiness, irritability, myoclonus, and brisk tendon jerks (Hyland 1993). In addition, there may be microcephaly, progressive neurologic deterioration, developmental delay, and convulsions (grand mal or myoclonic), the latter being more frequent in dihydropteridine reductase deficiency (Dhondt 1991). Many of these symptoms are also seen in aromatic--amino-acid decarboxylase deficiency or tyrosine hydroxylase deficiency (Blau et al 2001), conditions that also lead to gross deficiencies of the catecholamine neurotransmitters. In these diseases, plasma phenylalanine concentrations and biopterin and neopterin profiles are normal in CSF and plasma.

The autosomal dominantly inherited form of GTP cyclohydrolase deficiency (dopa-responsive dystonia) classically presents as a progressive dystonic gait disorder in childhood, with an average age of onset symptoms of 5 years to 6 years. The spectrum of clinical manifestations is; however, broad and may include a total absence of symptoms, minor muscle cramps, infantile or adult onset, an early nonprogressive course, delayed attainment of motor milestones, spastic diplegia, and the occurrence of parkinsonian-like features in later life (Nygaard 1993). A patient has also been described in whom the first symptom was an adult-onset oromandibular dystonia (Steinberger et al 1999); in others, presentation was with apparent primary torsion dystonia that was responsive to anticholinergic agents (Jarman et al 1997) or with a myoclonus-dystonia syndrome (Leuzzi et al 2002). Unfortunately, the mean time span between appearance of clinical symptoms and diagnosis is still more than 13 years worldwide (Tadic at al 2012).

Of those patients who present at the mean age with the typical dystonic gait disorder, 20% also have hyperreflexia and apparent extensor plantar responses, as well as other clinical features suggesting spasticity. These, together with the prominent upper motor neuron findings, including spastic diplegia, have in many cases led to an initial diagnosis of cerebral palsy (Nygaard et al 1994).

A diagnosis of dopa-responsive dystonia is generally considered because of a prior family history or the presence of a dystonic gait disorder, together with diurnal variation of symptoms. A response to levodopa obviously adds more weight to the diagnosis, but it is widely recognized that many dystonic and other movement disorders may respond to levodopa. In these cases the effect of levodopa eventually wears off. This is not the case in dopa-responsive dystonia, where there have not been any reports of a decrease in the effectiveness of the drug.

The measurement of homovanillic acid and 5-hydroxyindoleacetic acid, together with tetrahydrobiopterin and neopterin in cerebrospinal fluid can aid in differential diagnosis, because these metabolites have been decreased in all the cases of dopa-responsive dystonia, where they have been measured. Similar but more severe changes are found in the autosomal recessive GTP cyclohydrolase deficiency, and there is an associated hyperphenylalaninemia that is not found in dopa-responsive dystonia.

The analysis of pterins and neurotransmitter amine metabolites in CSF should also be considered in any child who does not have hyperphenylalaninemia, but has neurologic symptoms suggestive of an abnormality of tetrahydrobiopterin metabolism because defects specific to the central nervous system have been described for deficiencies of sepiapterin reductase, autosomal recessively inherited GTP cyclohydrolase 1, aromatic-L-amino-acid decarboxylase deficiency, or tyrosine hydroxylase deficiency (Furukawa et al 1998; Blau et al 2001).
Diagnostic workup

The possibility of a defect in tetrahydrobiopterin metabolism should be considered in all cases where hyperphenylalaninemia has been found on newborn screening, and also if characteristic neurologic signs develop in a child. Four separate procedures are used to identify the location of the defect in patients with hyperphenylalaninemia and to separate the tetrahydrobiopterin deficiencies from defects of phenylalanine hydroxylase: (1) analysis of pterins in urine, blood, CSF, or dried blood spots; (2) measurement of dihydropteridine reductase activity in fresh blood or from blood on filter-paper screening cards; (3) analysis of phenylalanine in plasma before and after a tetrahydrobiopterin loading test; and (4) analysis of pterins and neurotransmitter metabolites in CSF (Ponzone et al 1993; Hyland 1997; Blau et al 2001; Opladen et al 2011b).

The methods for urinary pterin analysis have been extensively reviewed (Hyland and Howells 1988). They rely on the appearance of characteristic pterin profiles from children affected with the different defects. These tests should be performed at elevated plasma phenylalanine concentrations (not with a low-phenylalanine diet). Liquid urine or urine on dried filter paper may be used. Urine is oxidized to convert all the reduced biopterin species (tetrahydro-; dihydro-; and quinonoid) to biopterin and reduced neopterin (dihydro-) to neopterin, and then the concentration of the total biopterin and neopterin is determined by fluorescence detection after HPLC separation. The use of dried blood spots on filter paper is more practical and allows for measurements of pterins, dihydropteridine reductase activity, and amino acids from a single specimen (Opladen et al 2011b). In all cases, concentrations of neopterin and biopterin are greatly reduced in GTP cyclohydrolase deficiency. Patients with 6-pyruvoyltetrahydropterin synthase deficiency have decreased biopterins with elevated neopterins, and those with dihydropteridine reductase deficiency have elevated biopterins with normal or slightly elevated neopterins. The pattern seen in dihydropteridine reductase deficiency is sometimes normal and sometimes similar to that seen in patients with hyperphenylalaninemia due to phenylalanine hydroxylase deficiency; therefore, definitive differential diagnosis can only be made by and must include direct measurement of dihydropteridine reductase activity in blood or from blood on filter-paper cards. In pterin-4 alpha-carbinolamine dehydratase deficiency, an additional peak of 7-biopterin, as opposed to the normal 6-biopterin, is detected.

The tetrahydrobiopterin loading test allows the detection of all patients with hyperphenylalaninemia and a recessively inherited defect in the biosynthesis of tetrahydrobiopterin, including patients with pterin-4 alpha-carbinolamine dehydratase deficiency. It should be performed prior to the introduction of a phenylalanine-reduced diet in all neonates with plasma phenylalanine concentration above 400 μmol/L (6.5 mg/dL). A positive diagnosis is made if plasma phenylalanine drops 4 to 8 hours following administration of 20 mg tetrahydrobiopterin per kg of body weight. This test is not always positive in dihydropteridine reductase deficiency. A combined phenylalanine and tetrahydrobiopterin loading test can discriminate between defects in tetrahydrobiopterin biosynthesis and dihydropteridine reductase deficiency (Ponzone et al 1993). Phenylalanine (100 mg/kg) is given orally, followed by 20 mg/kg tetrahydrobiopterin after 3 hours. With this regime, plasma phenylalanine concentrations return to normal within 4 hours following tetrahydrobiopterin administration in children with tetrahydrobiopterin synthesis defects. Patients with dihydropteridine reductase deficiency require an additional 4 hours to 6 hours before plasma phenylalanine normalizes. It should be noted that a decrease in plasma phenylalanine may also occur in some patients with mutations in the phenylalanine hydroxylase gene (Blau 2008).

Urine analysis of pterins and the tetrahydrobiopterin loading test are unable to distinguish between typical and atypical 6-pyruvoyltetrahydropterin synthase deficiency. The atypical forms still have phenylketonuria, demonstrating that tetrahydrobiopterin metabolism is abnormal peripheral; however, the concentrations of neurotransmitter metabolites (homovanillic acid and 5-hydroxyindoleacetic acid) are normal within CSF and neurologic symptoms remain absent in the majority of cases following correction of the hyperphenylalaninemia. Measurement of CSF neurotransmitter metabolites is, therefore, essential for differentiation between the 2 forms. In the cases where it has been measured, the concentrations of total biopterin in CSF are within the normal range, whereas total neopterin is elevated.

The autosomal dominantly inherited form of GTP cyclohydrolase deficiency (dopa-responsive dystonia), some compound heterozygotes with GTP cyclohydrolase deficiency (Furukawa et al 1998), and sepiapterin reductase deficiency (Bonafe et al 2001b) are not detected by newborn screening because of lack of overt hyperphenylalaninemia. Evidence for these 3 conditions can be obtained by the analysis of CSF because all cases investigated have had low concentrations of neurotransmitter metabolites and an abnormal pterin profile. An oral
phenylalanine-loading test (100 mg/kg) can be used to identify symptomatic and asymptomatic individuals with dopa responsive dystonia, sepiapterin reductase deficiency, and compound heterozygotes for GTP cyclohydrolase deficiency (Hyland et al 1997; Bonafe et al 2001b; Opladen et al 2011a). Monitoring of plasma phenylalanine and tyrosine concentrations with time shows a slower conversion of phenylalanine to tyrosine as compared to controls. Similar changes can be found in phenylketonuria heterozygotes, but again differentiation is possible by examination of pterins in blood or by mutation analysis. Biopterin concentrations rise under phenylalanine loading several fold above baseline (to >18 nmol/L), also in heterozygotes of phenylalanine hydroxylase deficiency, whereas in BH$_4$ deficiency, biopterin concentrations are and remain at low concentrations even following phenylalanine loading. Confirmation of the diagnosis of GTP cyclohydrolase deficiency can be established by finding a clinical response to levodopa, demonstration of low activity of GTP cyclohydrolase in mononuclear blood cells (Ichinose et al 1994) or cytokine stimulated fibroblasts (Bonafe et al 2001a) and identification of mutations in the GTP cyclohydrolase gene (Blau et al 2001). Additional evidence for sepiapterin reductase deficiency may be obtained by detection of elevated concentrations of sepiapterin in CSF and the diagnosis by the absence of sepiapterin reductase activity in cultured skin fibroblasts (Bonafe et al 2001b; Friedman et al 2012).

**Management**

The management of the autosomal recessively inherited abnormalities of tetrahydrobiopterin metabolism requires the correction of hyperphenylalaninemia when present, correction of the serotonin and catecholamine deficiency in the typical forms of the disease, and prevention of the onset of folate deficiency within the central nervous system in dihydropteridine reductase deficiency.

Strict control of plasma phenylalanine concentration is particularly important because phenylalanine also interferes with the passage of L-Dopa and 5-hydroxytryptophan across the blood-brain barrier, and fluctuation in plasma phenylalanine may, therefore, make control of the central neurotransmitter deficiency difficult. Normal plasma phenylalanine concentrations in GTP cyclohydrolase deficiency, 6-pyruvoyltetrahydropterin synthase deficiency, and pterin-4 alpha-carbolinolamine dehydratase deficiency can be maintained by administration of small doses of tetrahydrobiopterin (2 to 4 mg/kg per day). This therapy is preferable to the low-phenylalanine diet. Unfortunately, the use of tetrahydrobiopterin is generally not feasible for the treatment of hyperphenylalaninemia in dihydropteridine reductase deficiency. Large doses are required in the absence of this recycling enzyme (Kaufman 1986). Furthermore, in this disorder, BH$_4$ causes the accumulation of the potentially neurotoxic 7,8-dihydrobiopterin.

Precursor therapy with L-Dopa and 5-hydroxytryptophan, in conjunction with carbidopa (25% of L-Dopa daily dosage, if the total daily dose is below 400 mg/day, 10% of L-Dopa daily dosage if above 400 mg/day), a peripheral decarboxylase inhibitor, is the main treatment for the central deficiency of serotonin and the catecholamines (Hoffmann and Blau 2014). The doses required in each individual patient vary substantially, ranging from 1.7 to 20 for L-Dopa, 0.8 to 12 for 5-hydroxytryptophan, and 0.2 to 2.5 for carbidopa. The initial dose used should be low and should be gradually increased over a few weeks to the optimum. This optimum dose is established by measurement of neurotransmitter metabolites (homovanillic acid and 5-hydroxyindoleacetic acid) in CSF, by assessment of improvement or disappearance of neurologic symptoms when they exist, and by balancing these criteria with any side effects that may arise due to the therapy. Repeated lumbar puncture for neurotransmitter assessment is required. It is critical that this test be performed in a laboratory that has good age-related reference ranges for these metabolites, as metabolite concentration is rapidly decreased, especially in the period up to 1 year of age. Treatment is further complicated as 5-hydroxytryptophan can lead to anorexia, diarrhea, and tachycardia, and 5-hydroxytryptophan and L-Dopa compete for the same transporter site for their passage across the blood-brain barrier. Therefore, each antagonizes the passage of the other for entry into the brain.

Improved outcome has been described with a combination of monoamine oxidase inhibitors and neurotransmitter precursor therapy. Measurement of neurotransmitter metabolites to monitor therapy is less meaningful in this case; however, plasma prolactin concentrations provide a simple tool for treatment monitoring as dopamine is the essential inhibitory factor of prolactin secretion (Hoffmann and Blau 2014).

Combination of L-Dopa substitution with anticholinergic treatment (Trihexiphenidyl) or adjunctive treatment of L-Dopa substitution with inhibitors of monoamine oxidase B, such as Selegelin, and dopamine agonists, such as bromocriptine, may be helpful therapeutic combinations in some patients, but experience is very limited (Hoffmann and Blau 2014).

The central folate deficiency that arises in some cases of dihydropteridine reductase deficiency can lead to rapid
neurologic deterioration despite good control of plasma phenylalanine and treatment of the neurotransmitter deficiency with precursor therapy (Smith et al 1985). Treatment with folic acid is, therefore, recommended; 10-20 mg/day together with the above therapy may reverse or at least halt both the demyelinating processes and the calcification of the basal ganglia (Blau et al 2001; Hoffmann and Blau 2014). Treatment of the autosomal dominantly inherited GTP cyclohydrolase deficiency (dopa-responsive dystonia) requires correction of the nigrostriatal dopamine deficiency. Levodopa in conjunction with carbidopa is commenced at low dosage and titrated to achieve optimum levels.

**Special considerations**

**Pregnancy**

There is a single report of the outcome of pregnancy of a mother with autosomal recessively inherited tetrahydrobiopterin deficiency (Gizewska et al 2009). She was treated with neurotransmitter precursors and tetrahydrobiopterin during her pregnancy. Her first child was born at 31 weeks of gestation and had a right-sided, closed-lip schizencephaly with absence of septum pellucidum. Despite this, psychological development at 8 years of age was above average. Her second child had normal psychomotor development at the age of 5 years. Doparesponsive dystonia due to GTP cyclohydrolase deficiency is inherited in an autosomal dominant fashion; hence, there is a 50% chance of producing an affected fetus. Once diagnosis is made, treatment with levodopa is extremely effective and mental function does not appear to be compromised; therefore, prenatal diagnosis is not required.

**Anesthesia**

Therapy, especially substitution with L-Dopa/carbidopa, cannot be discontinued for several hours and must be provided intravenously, if oral intake is not possible.

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**References especially recommended by the author or editor for general reading.

Former authors
Keith Hyland PhD

ICD and OMIM codes
ICD codes

ICD-9:
Phenylketonuria: 270.1
Hyperphenylalaninemia: 270.1

ICD-10:
Classical phenylketonuria: E70.0
Other hyperphenylalaninemas: E70.1
- GTP cyclohydrolase deficiency
- 6-pyruvoyltetrahydropterin synthetase deficiency
- Pterin-4 alpha-carbinolamine dehydratase deficiency
- Dihydropteridine reductase deficiency
- Sepiapterin reductase deficiency

OMIM numbers
Phenylketonuria: #261600
GTP cyclohydrolase I deficiency: #233910
Dihydropteridine reductase deficiency: #261630
6-Pyruvoyltetrahydropterin synthase deficiency: #261640
Pterin-4α-carbinolamine dehydratase deficiency: #264070
Sepiapterin reductase deficiency: +182125
Dopa-responsive dystonia: #128230

Profile

Age range of presentation

0-01 month
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

Sex preponderance

female=male, 3-4 (GTP cyclohydrolase 1 deficiency Segawa disease, Dopa-responsive dystonia)
female=male, 1:1 (all other defects)

Family history

family history may be obtained

Heredity

heredity typical
autosomal recessive
autosomal dominant

Population groups selectively affected

none selectively affected

Occupation groups selectively affected
none selectively affected

**Differential diagnosis list**

- aromatic amino acid decarboxylase deficiency
- tyrosine hydroxylase deficiency
- phenylalanine hydroxylase deficiency

**Associated disorders**

- Chorea
- Developmental delay
- Dystonia
- Epilepsy
- Hypotonia
- Intellectual disability
- Phenylketonuria
- Seizures

**Other topics to consider**

- Aromatic L-amino acid decarboxylase deficiency
- Dopa-responsive dystonia
- Gene therapy of neurogenetic disorders
- Phenylketonuria