

Inherited Disorders Affecting Dopamine and Serotonin: Critical Neurotransmitters Derived from Aromatic Amino Acids¹⁻³

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Abstract

Many inherited disorders affecting aromatic amino acid metabolism have been described. This review will concentrate on the defects that lead to deficiencies of dopamine and serotonin within the central nervous system. Phenylalanine hydroxylase, tyrosine hydroxylase, and tryptophan hydroxylase all require tetrahydrobiopterin (BH4) as a cofactor. Inherited defects that reduce the concentration of BH4, therefore, in general, lead to phenylketonuria and to deficiencies of dopamine and serotonin, as tyrosine hydroxylase and tryptophan hydroxylase are the rate-limiting enzymes required for the synthesis of these neurotransmitters. Primary inherited defects of tyrosine hydroxylase and aromatic L-amino acid decarboxylase have also been described. The clinical phenotypes are very similar to those observed in patients with defects of BH4 metabolism. Differential diagnosis is critical as treatment is different in each of the disorders. To date, a primary deficiency of tryptophan hydroxylase has not been described; when it finally is, the clinical phenotype might surprise us, as many groups around the world have been searching for such a defect for a long time. *J. Nutr.* 137: 1568S–1572S, 2007.

The initial identification by Folling (1) of phenylalanine hydroxylase (PAH)⁴ deficiency as the cause of phenylketonuria led to a realization that an inherited disorder could lead to severe neurological disease and that the neurological symptoms could be prevented by the use of a low-phenylalanine diet. Since this initial ground breaking discovery, it has been recognized that defective phenylalanine metabolism can result not only through the effects of mutations in the PAH gene but may also arise because of a deficiency of the tetrahydrobiopterin (BH4) cofactor required for PAH activity. As well as its role in phenylalanine metabolism, BH4 is also a cofactor for the activities of tyrosine hydroxylase and tryptophan hydroxylase, the rate-limiting enzymes required for the synthesis of the catecholamine and serotonin neurotransmitters. Patients with BH4 deficiencies in

general, therefore, not only have phenylketonuria, but they also develop a severe deficiency of neurotransmitters within the central nervous system.

Inherited disorders of aromatic amino acid metabolism that affect neurotransmitter synthesis, other than those that involve phenylalanine metabolism, have also been described. Disorders of tyrosine hydroxylase and of aromatic L-amino acid decarboxylase (AADC) lead to clinical signs and symptoms that are very similar to those observed in patients with defects of BH4 metabolism. Differential diagnosis is critical, because treatment is different in each of the separate disorders. This chapter will describe the clinical phenotype and the methods of differential diagnosis that allow appropriate treatment to be initiated in the various disorders of dopamine and serotonin metabolism that are caused by inherited disorders that affect the metabolism of phenylalanine, tyrosine, and tryptophan.

Disorders of BH4 metabolism

BH4 is the obligatory cofactor required for the activity of PAH that converts phenylalanine to tyrosine in liver and kidney. The cofactor is synthesized from GTP in a 3-step reaction and following its reduction in the hydroxylation reaction, it is reduced back to the active form via the action of pterin 4 α -carbinolamine dehydratase and dihydropteridine reductase (Fig. 1). Inherited disorders have been described that affect each of the steps involved in the synthesis and recycling of BH4. Recessively inherited defects of GTP cyclohydrolase (2), 6-pyruvoyltetrahydropterin synthase (3), pterin 4 α -carbinolamine dehydratase (4), and dihydropteridine reductase (5) all lead to hyperphenylalaninemia and are therefore detected at the time of newborn

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⁴ Abbreviations used: AADC, aromatic L-amino acid decarboxylase; BH4, tetrahydrobiopterin; CSF, cerebrospinal fluid; 5HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid; PAH, phenylalanine hydroxylase.

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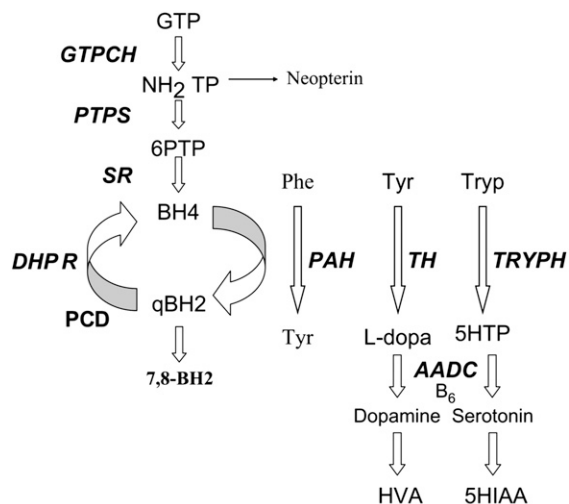


FIGURE 1 Synthesis and catabolism of dopamine and serotonin. Dopamine and serotonin are formed from the amino acids tyrosine and tryptophan, respectively. Their synthesis also requires 2 cofactors. BH4 is formed in a 3-step pathway from GTP and is the cofactor for tyrosine hydroxylase and tryptophan hydroxylase. It is also required for the activity of PAH. The second cofactor is pyridoxal 5'-phosphate, which is required for AADC activity. Following release of dopamine and serotonin, they are rapidly metabolized to form HVA and 5HIAA, respectively, and these metabolites are measured in spinal fluid and provide an indication of the overall turnover of these neurotransmitters. GTPCH, GTP cyclohydrolase; 6PTPS, 6-pyruvoyltetrahydropterin synthase; SR, sepiapterin reductase; PCD, pterin α -carbinolamine dehydratase; DHPR, dihydropteridine reductase; TH, tyrosine hydroxylase; NH_2TP , dihydroneopterin triphosphate; 6PTP, 6-pyruvoyltetrahydropterin; qBH2, quinonoid dihydrobiopterin; 7,8-BH2, 7,8-dihydrobiopterin; Phe, phenylalanine; Tyr, tyrosine; Tryp, tryptophan; TH, tyrosine hydroxylase; TRYPH, tryptophan hydroxylase; 5HTP, 5-hydroxytryptophan; B₆, pyridoxal 5'-phosphate.

screening. Follow-up testing of urine pterins (biopterin and neopterin) and measurement of dihydropteridine reductase activity in blood is then required to pinpoint the position of a particular defect (6). Dominantly inherited GTP cyclohydrolase deficiency, some compound heterozygotes for GTP cyclohydrolase deficiency, and sepiapterin reductase deficiency do not lead to hyperphenylalaninemia (7,8) and consequently are missed on newborn screening. Pterin patterns in urine are also frequently normal, but in cerebrospinal fluid (CSF), the pterin pattern is characteristic for each disorder (Table 1).

BH4 is also required for the activity of tyrosine hydroxylase and tryptophan hydroxylase, which are the rate-limiting enzymes required for the synthesis of dopamine and serotonin, respectively (Fig. 1). The products of these reactions are L-dopa and 5-hydroxytryptophan and these are subsequently decarboxylated by AADC to form the active neurotransmitters. Dopamine and serotonin are rapidly metabolized to form homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5HIAA), respectively, and the measurement of these metabolites in CSF is used to estimate the overall turnover of the neurotransmitters within the brain. The inherited disorders affecting BH4 metabolism, in general, lead to severe deficiencies of both dopamine and serotonin within the central nervous system. The exceptions are dominantly inherited GTP cyclohydrolase deficiency, where only dopamine metabolism is affected, and pterin 4 α -carbinolamine dehydratase deficiency and milder forms of 6-pyruvoyltetrahydropterin synthase deficiency, where neurotransmitter metabolism appears normal (6).

Clinical symptoms associated with disorders of BH4 with hyperphenylalaninemia. The clinical signs and symptoms found in the severe deficiencies of GTP cyclohydrolase, 6-pyruvoyltetrahydropterin synthase, and dihydropteridine reductase are similar. In the neonatal period, these are related to the presence of hyperphenylalaninemia and to the severe neurotransmitter deficiency. There may be poor suck, decreased spontaneous movements, floppiness, irritability, and microcephaly. After ~2 mo, a more severe picture surfaces with the presence of oculogyric crises, hypersalivation, temperature disturbance in the absence of infection, pinpoint pupils, hypokinesia, ptosis of the eyelids, swallowing difficulties, seizures (grand mal or myoclonic), continuing irritability, and developmental delay (9).

In peripheral forms of 6-pyruvoyltetrahydropterin synthase deficiency and pterin α -carbinolamine dehydratase deficiency, neurotransmitter synthesis is not affected and in these cases, neurological symptoms are mild or absent once the hyperphenylalaninemia has been corrected (6).

Clinical symptoms associated with disorders of BH4 metabolism without hyperphenylalaninemia.

Dominantly inherited GTP cyclohydrolase deficiency. The first symptoms, occurring at ~5–6 y of age, are generally a dystonic posture of the foot with muscle dystonia spreading to the other extremities within several years. However, the phenotype is extremely variable. Occasionally, onset has been with writer's cramp, arm dystonia, retrocollis, torticollis, poor coordination, or slowness in dressing before the development

TABLE 1 Metabolite patterns observed in urine, plasma, and CSF in the inherited disorders affecting dopamine and serotonin metabolism

	Phe	BH4	BH2	Neop	Sep	Prim	HVA	5HIAA	3OMD
GTPCH (Recessive)	↑ (P)	↓ (U, CSF)	N	↓ (U, CSF)	N	N	↓ (CSF)	↓ (CSF)	N
GTPCH (Dominant)	N	↓ (CSF)	N	↓ (CSF)	N	N	↓ (CSF)	± ↓ (CSF)	N
6PTPS	↑ (P)	↓ (U, CSF)	N	↑ (U, CSF)	N	N	↓ (CSF)	↓ (CSF)	N
6PTPS (Mild)	↑ (P)	↓ (U)	N	↑ (U)	N	N	N	N	N
SR	N	↓ (CSF)	↑ (CSF)	N	↑ (CSF)	N	↓ (CSF)	↓ (CSF)	N
PCD	↑ (P)	↓ (U)	N	N	N	↑ (U)	N	N	N
DHPR	↑ (P)	↓ (U) ± ↓ (CSF)	↑ (U, CSF)	N	N	N	↓ (CSF)	↓ (CSF)	N
TH	N	N	N	N	N	N	↓ (CSF)	N	N
AADC	N	N	N	N	N	N	↓ (CSF)	↓ (CSF)	↑ (P, CSF, U)

GTPCH, GTP cyclohydrolase; 6PTPS, 6-pyruvoyltetrahydropterin synthase; SR, sepiapterin reductase; PCD, pterin α -carbinolamine dehydratase; DHPR, dihydropteridine reductase; TH, tyrosine hydroxylase; Phe, phenylalanine; BH2, 7, 8-dihydrobiopterin; neop, neopterin; SEP, sepiapterin; Prim, primapterin; 3OMD, 3-O-methyldopa; N, normal; ↓, decreased; ↑, elevated; P, plasma; U, urine.

of leg signs (10). The symptoms often, but not always, show a marked diurnal variation. Of those patients who present at the average age with the typical dystonic gait disorder, 20% also have hyperreflexia and apparent extensor plantar responses, as well as other clinical features suggesting spasticity. There is a sex-influenced, reduced penetrance of disease phenotype, with penetrance estimates of 15% in men and 45% in women. In older patients, major depressive disorder and obsessive-compulsive disorder are seen more frequently than the rate observed in the general population (11).

Compound heterozygotes with GTP cyclohydrolase deficiency. Two compound heterozygotes with GTP cyclohydrolase deficiency have been described in whom hyperphenylalaninemia was not present (12). One presented at 6 mo of age with developmental motor delay, abnormal muscle tone, truncal hypotonia, and poor head control together with intermittent dystonic extension of the legs, symmetrical hyperreflexia, and bilateral extensor plantar responses progressing by 1 y to generalized dystonia, episodes of paroxysmal dystonic limb spasms, and oculogyric crises. The other had a clinical course typical of dominantly inherited GTP cyclohydrolase deficiency.

Sepiapterin reductase deficiency. Clinical symptoms have included seizures, dyskinesia, athetosis, dystonia, hyperkinesia, choreoathetosis, hypotonia, and hypersomnolence (8). Hyperphenylalaninemia is absent in sepiapterin reductase deficiency, as other reductases are present in the liver that can substitute for this enzyme. These enzymes are not present in the brain, which results in a lack of BH₄ and subsequent neurotransmitter deficiency.

Treatment of the BH₄ deficiencies. Treatment is dependent on the site of the enzyme deficiency and is designed to increase central neurotransmitter levels and to decrease phenylalanine levels in the cases where hyperphenylalaninemia is present. In the recessive deficiencies of GTP cyclohydrolase and 6-pyruvoyltetrahydropterin synthase, plasma phenylalanine levels can be reduced by administration of BH₄. This approach does not work in dihydropteridine reductase deficiency, because in the absence of recycling, one molecule of BH₄ is required for each molecule of phenylalanine that is converted into tyrosine. Instead, a low-phenylalanine diet is used to control phenylalanine levels. Folinic acid therapy is also required in dihydropteridine reductase deficiency, because a central folate deficiency can arise due to an inhibition of the production of 5-methyltetrahydrofolate (13).

BH₄ does not easily cross the blood brain barrier and cannot be used to correct the central neurotransmitter deficiency in any of the BH₄ deficiencies. This is achieved by administering L-dopa and 5-hydroxytryptophan, which by-pass the metabolic block and are converted to dopamine and serotonin. These precursors are normally given together with carbidopa, which is a peripheral AADC inhibitor. This prevents peripheral decarboxylation of the precursors and allows more to enter the brain.

The required dose of L-dopa/carbidopa has varied from 1 to 3 mg/kg 3–4 times/d in infancy rising to 8–10 mg/kg 3–4 times/d after 2 y of age. For 5-hydroxytryptophan, the dose has varied from 1 to 2 mg/kg 3–4 times/d in infancy rising to 6–8 mg/kg 3–4 times/d after 2 y of age (14). Adjunct therapy with Deprenyl (selective monoamine oxidase B inhibitor) has been used with some success, allowing reduction of the administered precursors by preventing catabolism of the neurotransmitters. The effectiveness of treatment is monitored by the clinical outcome and by testing of CSF to determine whether neurotransmitter metabolite levels (HVA and 5HIAA) have normalized.

Tyrosine hydroxylase deficiency

Tyrosine hydroxylase is the first and rate-limiting step in catecholamine biosynthesis (Fig. 1). All cases reported so far have had an autosomal recessive inheritance. Several phenotypes for this disorder have been described, including a progressive gait disorder similar to that seen in dominantly inherited GTP cyclohydrolase deficiency, an infantile parkinsonism picture, a form with a hypotonic, ataxic phenotype and a severe, early onset encephalopathy. An excellent review describing the different forms of tyrosine hydroxylase deficiency has been published (15). It should be emphasized that in most cases described, the phenotype is not one of dystonia but rather a mostly progressive, often lethal neurometabolic disorder presenting in early infancy.

Treatment of tyrosine hydroxylase deficiency. Treatment in all the phenotypes is initially with low dose L-dopa/carbidopa. In some cases, improvement may be immediate and in others response may be slow and progressive over months. Outcome to some degree depends on the severity of the presenting clinical phenotype. Tyrosine hydroxylase-deficient patients are especially prone to side effects of dyskinesia and extreme irritability even at very low doses. Selegiline has been added in addition to Sinemet to prevent breakdown of any neurotransmitters formed. Adjunct therapies have included trihexyphenidyl, amantidine, laxatives, and antireflux agents.

Aromatic L-amino acid decarboxylase deficiency

Clinical symptoms in AADC deficiency generally appear after the first few months of life and in most cases are similar to those seen in the autosomal recessive forms of BH₄ deficiency. They include truncal hypotonia, limb hypertonia, severe irritability, increased startle, and some kind of movement disorder, with oculogyric crises, limb dystonia, athetosis, and paucity of movement being found in most patients. These may occur together with ocular convergence spasm, myoclonic jerks, orofacial dystonia, head drop, torticollis, postural or action tremor, blepharospasm or flexor spasms. Autonomic symptoms have included ptosis, miosis, paroxysmal sweating, nasal congestion, temperature instability, hypotension, and gastroesophageal reflux. Endocrine abnormalities, including tendency to hypoglycemia, elevated prolactin levels, and growth deficiency, have also been reported (16). Milder forms of the disorder have also been described (17,18).

A secondary deficiency of AADC resulting from a lack of pyridoxal 5'-phosphate has been documented (19). The biochemical pattern mimics that seen in AADC deficiency and, in addition, there are elevations of threonine and glycine, amino acids that require pyridoxal 5'-phosphate for their catabolism. These patients have a severe neonatal epileptic encephalopathy and the lack of pyridoxal 5'-phosphate occurs, because there is an inherited deficiency of pyridox(am)ine 5'-phosphate oxidase (19). Oral therapy with pyridoxal 5'-phosphate has stopped the seizures in the cases where it has been tried. (19,20).

Treatment of AADC deficiency. All cases of AADC deficiency reported have had severe deficiencies of both serotonin and dopamine; however, there has always been some residual production of these neurotransmitters, because small concentrations of HVA and 5HIAA can be found in CSF. Treatment is therefore designed to try to maintain levels of any dopamine or serotonin produced and to stimulate dopaminergic neurotransmission. This has been achieved using dopamine agonists (pergolide, bromocriptine, and pramipexole) and monoamine oxidase inhibitors (tranylcypamine and selegiline) (16,21). In a

single family with a mutation that affects the binding of L-dopa to AADC, a response to L-dopa has been observed (22). AADC requires pyridoxal 5'-phosphate as a cofactor. A pyridoxal 5'-phosphate-responsive form of AADC has not yet been described but a trial with this cofactor should always be attempted in new patients. In many cases, adjunct therapy with folinic acid is required. This is needed because AADC deficiency leads to accumulation of L-dopa, which is methylated to form 3-O-methyldopa (Fig. 1). The methyl group originates from 5-methyltetrahydrofolate, which can become depleted (23). For this reason, 1 carbon metabolism should be investigated in patients with AADC deficiency and, if indicated, therapy with folate replacement commenced.

Differential diagnosis

Differential diagnosis between the above conditions relies on the measurement of plasma phenylalanine, pterins in urine, and pterins and HVA, 5HIAA, and 3-O-methyldopa in CSF. The patterns found in each disorder are shown in Table 1. For the disorders of BH4 metabolism, 3 separate procedures are used to identify the location of the defect and to separate the deficiencies from the primary defects of PAH: 1) analysis of pterins in urine, 2) measurement of dihydropteridine reductase activity in blood, and 3) analysis of phenylalanine in plasma before and after a BH4 loading test (24,25). Measurement of urine pterins should be performed at elevated plasma phenylalanine levels (not under a low-phenylalanine diet) and either 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 after HPLC separation (26). Neopterin and biopterin concentrations are greatly reduced in GTP cyclohydrolase deficiency (2), 6-pyruvoyltetrahydropterin synthase deficiency leads to low levels of biopterins and elevated neopterins (27), and in dihydropteridine reductase deficiency there are elevated biopterins with normal or slightly elevated neopterins (6). The pattern in dihydropteridine reductase deficiency is similar to that seen in patients with hyperphenylalaninemia due to PAH deficiency; therefore, definitive differential diagnosis can only be made by direct measurement of dihydropteridine reductase activity in blood or from blood on Guthrie cards. An additional peak of 7-biopterin (as opposed to the normal 6-biopterin) is detected in pterin-4 α -carbinolamine dehydratase deficiency and is diagnostic for this condition (28). These same patterns are seen if pterins are analyzed in CSF.

The BH4 loading test allows the detection of all patients with a defect in the biosynthesis of BH4, including those in whom there is only a partial deficiency (25). This test is not always positive in dihydropteridine reductase deficiency and false positives can occur, because the hyperphenylalaninemia resulting from a primary deficiency of PAH can in many cases be ameliorated following BH4 administration (29).

Urine analysis of pterins and the BH4 loading test are unable to distinguish between mild and severe 6-pyruvoyltetrahydropterin synthase deficiency. The mild forms still have phenylketonuria; however, the concentrations of neurotransmitter HVA and 5HIAA are normal within CSF and neurological symptoms are absent following correction of the hyperphenylalaninemia.

Autosomal dominantly inherited GTP cyclohydrolase deficiency, compound heterozygotes with GTP cyclohydrolase deficiency, and sepiapterin reductase deficiency do not lead to hyperphenylalaninemia and diagnosis can be made only by CSF analysis (7,8). All have low levels of HVA and 5HIAA. The GTP

cyclohydrolase deficiencies also have low levels of neopterin and biopterin, whereas the sepiapterin reductase deficiency leads to high levels of total biopterin, increased neopterin, and increased sepiapterin. An oral phenylalanine loading test can also help identify these patients (8,30). Similar changes can be found in phenylketonuria heterozygotes, but the 2 situations can be differentiated by repeating the load with prior administration of BH4. Confirmation of the diagnosis of GTP cyclohydrolase deficiency can be established by enzyme assay in cytokine-stimulated fibroblasts (31) and that of sepiapterin reductase deficiency by enzyme assay in unstimulated fibroblasts (8).

Pterin metabolism is not altered in the inherited disorders affecting tyrosine hydroxylase and AADC. These conditions are detected via changes in neurotransmitter metabolites in CSF. Tyrosine hydroxylase deficiency leads to an isolated decrease in HVA. Unfortunately, a drop in HVA is not specific for tyrosine hydroxylase deficiency (32); hence, definitive diagnosis has to rely on detection of pathogenic mutations. A deficiency of AADC leads to a very characteristic pattern in CSF. Both HVA and 5HIAA are decreased and there is an elevation of the precursors L-dopa and 5-hydroxytryptophan. The L-dopa is further metabolized to form 3-O-methyldopa, which also accumulates in CSF, urine, and plasma (33). 3-O-Methyldopa can be further metabolized to vanillic acid, which can be detected in urine on an organic acid screen if looked for carefully.

Phenylketonuria was recognized as an inherited disorder in the early 1930s (1). It required 20 y to show that it was caused by decreased liver PAH activity (34) and another 20 y before researchers realized that defective metabolism of BH4 could also lead to elevated phenylalanine levels (5,35). Since then, defects in all the known components involved in BH4 biosynthesis and catabolism have been described (6) and it was shown that the BH4 deficiencies, in general, caused a severe deficiency of the dopamine and serotonin neurotransmitters within the brain, resulting from decreased activity of tyrosine and tryptophan hydroxylase. The concept of inherited disorders that affect dopamine and serotonin metabolism led to the search for other defects in their synthesis. Aromatic L-amino acid decarboxylase deficiency was first described in 1990 (36) and a primary deficiency of tyrosine hydroxylase in 1996 (37). A primary deficiency of tryptophan hydroxylase has never been described. Several groups around the world have been actively searching for such a defect for many years. When it is eventually found, the clinical phenotype is likely to surprise us.

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