

Inherited disorders of amine biosynthesis

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Amine biosynthetic defects that result in dopamine deficiency encompass an increasingly broad spectrum of neurological phenotypes. This review highlights observations from the literature in addition to the author's personal perspectives from ongoing studies of individuals and families with a select subset of these disorders: aromatic L-amino acid decarboxylase deficiency and dopa-responsive dystonia due to guanidine triphosphate cyclohydrolase 1 and tyrosine hydroxylase deficiencies. These disorders, while demonstrating a shared dopamine deficiency state, highlight the complexities of the dopaminergic pathways in relation to variables including gender, circadian variation in neurotransmitter levels, receptor expression and neurological development. An improved understanding of the mechanisms involved in phenotypic expression and responses to treatment in inborn errors of amine biosynthesis will undoubtedly lead to advances in our understanding and treatment of more complex and common neurological disorders, such as Parkinson's disease.

The term 'neurotransmitter disorders' encompasses a group of conditions characterized by defects in the production, transport, release and reuptake of chemical compounds involved in neurotransmission. Defects in amine biosynthesis represent a subset of disorders associated with variable deficiencies of serotonin, dopamine, norepinephrine and epinephrine (Figure 1). Amines are critical in a variety of signaling pathways in the central and peripheral nervous systems, and play a direct role in the regulation of movement and activity levels, mood, attention, responses to stress and sleep. Amine-deficiency states are associated with diverse neurological manifestations with widely variable expressivity and age of onset. This article reviews observations in three disorders, linked by a shared defect in dopamine synthesis yet representative of the diverse range of neurological symptoms and treatment challenges in this group of disorders: aromatic L-amino acid decarboxylase (AADC) deficiency, guanidine triphosphate (GTP) cyclohydrolase (GTPCH) deficiency and tyrosine hydroxylase (TH) deficiency. The absence of elevated plasma phenylalanine precludes the identification of these disorders via current newborn screening protocols, thus placing the burden of diagnosis squarely on the neurologist. Distinguishing features, including pattern of inheritance, severity and signature of the associated neurotransmitter deficiencies, presence or absence of associated cognitive and developmental impairments and variable response to current treatment approaches, help highlight the complex variables regulating dopaminergic

neurotransmission. Insights gained from observations in these disorders demonstrate the importance of dopamine signaling in neurodevelopment, the role of gender in moderating phenotypes, circadian variations in neurotransmission and the challenges in providing optimal therapeutic outcomes.

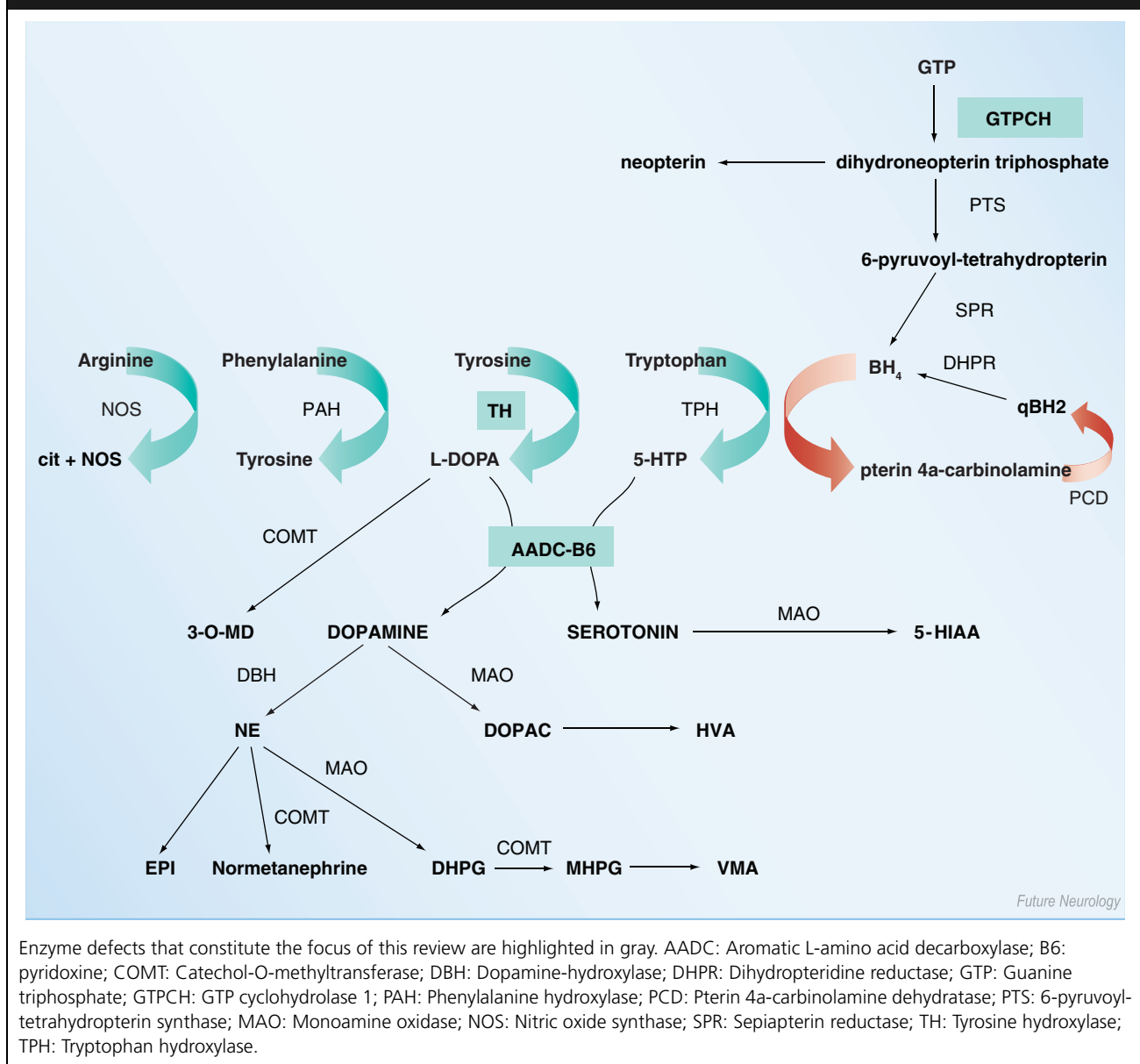
Neurological symptoms associated with inborn errors of dopamine synthesis span an increasingly broad range of phenotypes, from subtle alterations in mood or gait to a severe infantile Parkinsonism syndrome. The classic childhood-onset gait disorder, first recognized by Segawa as a 'dopa-responsive dystonia' more than 3 decades ago, is the most well known of these disorders. The diagnosis and treatment of individuals with dopa-responsive dystonia remains one of the most rewarding experiences in neurology – leading to a dramatic transformation in the lives of our patients, often over just a few weeks. By contrast, we face a host of obstacles in providing effective treatments for the large majority of patients with AADC deficiency, and in a subset of patients with TH deficiency. An overview of the amine biosynthetic pathway is shown in Figure 1.

The identification of amine disorders that are not associated with defects in phenylalanine metabolism (and thus can not be ascertained via newborn screening) occurs primarily by recognition of key neurological symptoms. Table 1 lists the subset of amine defects not associated with elevated phenylalanine levels; those with an associated dopamine-deficiency state are highlighted in bold.

Keywords: aromatic L-amino acid decarboxylase deficiency, dopa-responsive dystonia, guanidine triphosphate cyclohydrolase 1 deficiency, infantile parkinsonism, neurotransmitter deficiency disorders, Segawa's syndrome, tyrosine hydroxylase deficiency

future
medicine

Figure 1: Synthesis and catabolism of amine neurotransmitters.



Enzyme defects that constitute the focus of this review are highlighted in gray. AADC: Aromatic L-amino acid decarboxylase; B6: pyridoxine; COMT: Catechol-O-methyltransferase; DBH: Dopamine-hydroxylase; DHPR: Dihydropteridine reductase; GTP: Guanine triphosphate; GTPCH: GTP cyclohydrolase 1; PAH: Phenylalanine hydroxylase; PCD: Pterin 4a-carbinolamine dehydratase; PTS: 6-pyruvoyl-tetrahydropterin synthase; MAO: Monoamine oxidase; NOS: Nitric oxide synthase; SPR: Sepiapterin reductase; TH: Tyrosine hydroxylase; TPH: Tryptophan hydroxylase.

Dystonic gait, particularly if it is associated with diurnal variation, or childhood-onset Parkinsonism are more likely to be associated with a dopamine deficiency state. However, the wide spectrum of phenotypes associated with dopamine deficiency and the overlap with other movement disorders and conditions can make accurate identification and diagnosis of these disorders challenging. The routine availability of increasingly sophisticated diagnostic tools, including cerebrospinal fluid (CSF) neurotransmitter metabolite and biopterin profiling, urine biopterin studies, neuroimaging studies, phenylalanine loading studies, enzymatic assays in blood

cells or skin fibroblasts and molecular studies, have greatly increased our ability to accurately diagnose and treat patients in a timely fashion.

Segawa's syndrome: autosomal dominant 'dopa-responsive dystonia'

The most well described and widely identified entity among this group of disorders is autosomal dominant dopa-responsive dystonia, caused by GTPCH1 deficiency, also known as Segawa's syndrome [1]. Patients with the classic dystonic gait disorder, associated with worsening late in the day and often exacerbated by activity, are not difficult to recognize. This diagnosis

Table 1. Inborn errors of amine synthesis and metabolism with normal plasma phenylalanine levels.*

Enzyme	Neurological symptoms	Locus/gene	Inheritance
GTPCH	Dystonic gait disorder with diurnal variation, writer's cramp, restless leg syndrome and tremor	14q22.1–22.2 <i>GCHI</i>	AD
AADC	Dystonia, spasticity, torticollis, axial hypotonia, limb rigidity, autonomic symptoms, psychomotor retardation, ptosis, oculogyric crises	7p11 <i>AADC</i>	AR
SPR	Parkinsonian symptoms, ptosis, psychomotor retardation, behavioral disturbances	2p14p12 <i>SPR</i>	AR
TH	Gait disturbance, infantile parkinsonism, dystonia, speech delay, hypotonia, ptosis	11p15.5 <i>TH</i>	AR
DBH	Orthostatic hypotension, lethargy, ptosis	9q34 <i>DBH</i>	
MAO-A	Mild mental retardation, tendency for violent or aggressive behavior	Xp11.23 <i>MAO-A</i>	XR

*Disorders associated with dopamine deficiency depicted in bold.

AADC: Aromatic L-amino acid decarboxylase; AD: Autosomal dominant; AR: Autosomal recessive; DBH: Dopamine β hydroxylase;

GTP: Guanine triphosphate; GTPCH: GTP cyclohydrolase; MAO-A: Monoamine oxidase A; SPR: Sepiapterin reductase; TH: Tyrosine hydroxylase;

XR: X-linked recessive.

should also be considered in patients with spastic diplegia, particularly if diurnal fluctuation of symptoms is present. In addition, an increasingly wide spectrum of more atypical symptoms has been recognized in familial cases, including writer's cramp, asymmetric limb dystonia, tremor and mood and sleep disorders [2]. In patients with a classic presentation, clinicians often make a presumptive diagnosis following remission of symptoms with a treatment trial of L-dopa/carbidopa.

Although inheritance is autosomal dominant, penetrance is incomplete, and variable expressivity among family members with the same mutation is well-documented [3,4]. For instance, one might see spastic diplegia, writer's cramp, isolated tremor, or more typical dystonic gait phenotypes among different members of the same family. The female-to-male ratio in sporadic cases is 4:1, and investigators have confirmed increased penetrance of *GCHI* mutations in females [5,6].

Not surprisingly, mood and sleep disorders appear to be prevalent in families with the disorder, although these issues have not been studied systematically. Preliminary data in an ongoing study of prospectively ascertained family members support an increased burden of attentional difficulties, anxiety, dysphoria, depression and sleep disorders.

CSF neurotransmitter metabolite and biopterin studies are helpful in confirming the diagnosis in these patients, and can help characterize the degree of associated dopamine and

serotonin deficiency. Phenylalanine loading can be valuable in confirming a suspected diagnosis, but is not specific to the disorder as phenylketonuria (PKU) heterozygotes also manifest delayed phenylalanine clearance. GTPCH activity can be measured directly in skin fibroblasts. If possible, CSF analysis should be performed before institution of a treatment trial of L-dopa/carbidopa, since treatment results in increased levels of homovanillic acid (HVA) and 3-O-methyldopa. The typical pattern in CSF in dopa-responsive dystonia due to GTPCH deficiency is a low HVA level, a normal or low serotonin (5-HIAA) level and reduced tetrahydrobiopterin (BH₄) levels. Patients who are heterozygous for a *GCHI* mutation, despite their normal blood phenylalanine levels on routine screening, can be shown to have abnormal phenylalanine metabolism if stressed by administration of an oral phenylalanine load. If cytokine-stimulated fibroblast enzyme analysis of biopterin metabolism is not feasible or patients decline a CSF examination and have an otherwise atypical presentation, an oral phenylalanine loading test may be helpful in supporting the diagnosis. Phenylalanine is administered orally to the fasting patient at a dose of 100 mg/kg. Serum phenylalanine and tyrosine levels are obtained at baseline, and 1, 2 and 4 h post-loading. An elevated phenylalanine–tyrosine ratio and delayed clearance of phenylalanine are typical in patients with GTPCH deficiency, since BH₄ levels are typically reduced. Gene

sequencing for *GCHI* is available for confirmation of diagnosis and may be a valuable adjunct to biochemical diagnostic studies. However, sequencing alone should not be used to exclude the diagnosis, since complete sequencing of coding regions and splice sites detects mutations in only approximately 60% of patients [7,8]. Additional screening, including quantitative PCR techniques to identify exonic deletions, can increase the rate of detection to as high as 87% [9]. It may be difficult to distinguish patients with dopa-responsive dystonia owing to GTPCH deficiency or milder forms of TH or sepiapterin reductase (SR) deficiency [10]. CSF neurotransmitter and biopterin studies can be helpful in these circumstances to help determine likely etiology prior to proceeding to mutation analysis, which is more costly.

To date, most mutations in *GCHI* have been documented in association with autosomal dominant dopa-responsive dystonia. These patients, in addition to compound heterozygotes with an intermediate phenotype, have some preservation of GTPCH activity in the liver, enough to maintain normal phenylalanine levels under usual circumstances. CSF neurotransmitter metabolite and biopterin analysis reveals a fairly specific signature, with low levels of HVA, 5-HIAA, neopterin and biopterin levels, although such abnormalities can be seen secondarily in certain circumstances, including neurodegenerative conditions or in those with a history of hypoxic–ischemic encephalopathy. By contrast, patients described in the literature with the autosomal recessive form of GTPCH deficiency present with elevated phenylalanine levels in the newborn period. At the most severe end of the spectrum, such patients demonstrate severe global developmental impairment, marked hypotonia of axial muscles, involuntary eye movement abnormalities, fluctuating limb hypertonia or dystonia, seizures and autonomic symptoms, including temperature dysregulation, excessive diaphoresis and blood pressure instability. They typically have absent GTPCH activity in blood cells, liver and skin fibroblasts. Rare mutations are associated with both dominant and recessive phenotypes [11]. A subset of severely affected infants and children demonstrating the classic CSF profile and enzyme deficiency in cytokine-stimulated fibroblasts fail to show elevated phenylalanine levels or mutations in the *GCHI* gene. Thus, the mechanism of GTPCH deficiency in these patients deserves further study.

Tyrosine hydroxylase deficiency: autosomal recessive dopa-responsive dystonia

TH deficiency, sometimes referred to as ‘autosomal recessive Segawa’s syndrome’, displays a diverse phenotype, ranging from a progressive dystonic gait disturbance and tremor in childhood to severe infantile parkinsonism [12–14]. A wide range of symptoms can be associated with TH deficiency, linked with mild, moderate and severe phenotypes.

In the mildest cases, walking or running may be clumsy but little else may be noticed, at least initially. Abnormal posturing may be evident when the child is stressed, or later in the day. These symptoms may progress slowly as the child gets older. Occasionally, one side of the body may seem weaker, or the child may begin to toe-walk because of hamstring or heel-cord tightness. Sometimes these children are diagnosed with cerebral palsy; other times they are simply considered clumsy. Some children demonstrate attention difficulties or mild articulation disorders. Essentially, all children with mild symptoms are readily treated with medication.

In moderately affected cases, children demonstrate an abnormal gait and may demonstrate dystonic posturing while walking, or with attempts to walk on their heels or toes. Some children appear ataxic, or have significant spasticity; speech delay may be present. Many of these children are diagnosed with cerebral palsy. Some demonstrate involuntary eye movements, characterized by either brief upward eye-rolling movements when fatigued or stressed or frank oculogyric crises. The majority of these children have an excellent response to treatment, but full benefit may take many months.

In the most severe cases, children are profoundly disabled from early infancy. This is referred to as the infantile Parkinson’s disease variant. Infants may demonstrate muscle rigidity, bradykinesia, arching, tremor, poor voluntary muscle control, involuntary eye movements and psychomotor delay. They may have ptosis. They usually have speech delay and often demonstrate difficulties feeding, chewing or swallowing. Constipation is also common. While most children demonstrate increased muscle tone and even rigidity, there are children who have generalized low muscle tone, with poor head control and an inability to sit unsupported; they often demonstrate torticollis. They may have difficulty directing their hands to a toy, generating a flinging arm motion. Occasionally, children suffer

from intermittent color changes, unexplained low body temperature or fevers, low blood sugar and difficulty regulating blood pressure. These symptoms are more likely to occur during another illness the child may be experiencing. Children in this severely affected group of patients are more difficult to treat, and several medications may be required to modulate symptoms. They are unusually vulnerable to the side effects of dopaminergic agonists or precursors, which can result in excessive movement and irritability. Response may be slow, with some continued benefit over months to years, but may not result in the complete resolution of all symptoms. Some children have had persistent encephalopathy and motor disability in spite of directed treatment of their underlying dopamine deficiency state [15].

Low TH activity results in significant CSF catecholamine deficiency, as demonstrated by low HVA concentrations; CSF concentrations of 5-HIAA, neopterin and biopterin are normal. It is more difficult to distinguish these children from secondary neurotransmitter deficiency states, since phenylalanine loading studies are normal and enzymatic assays for confirmation of a suspected diagnosis are not presently available. Confirmation via molecular testing is extremely helpful, particularly in providing adequate counseling for parents regarding the risk of recurrence with future pregnancies. While clinical testing for gene sequencing is currently unavailable in the USA, it is available via laboratories in Europe [101]. Children have a paucity of autonomic features, suggesting a compensatory peripheral mechanism, except in children with the severe infantile parkinsonism variant. In four patients whom the author has observed, including one patient with the severe infantile parkinsonism variant, peripheral plasma catecholamine levels have been normal, although reduced urine HVA levels have been noted. Caution should be taken to monitor blood glucose in the setting of prolonged fasting, such as prior to a magnetic resonance imaging study.

Patients' responses to L-dopa/carbidopa vary, and some have complete reversal of symptoms. The exception to this is the patient with the severe infantile parkinsonism form. These patients sometimes tolerate L-dopa poorly, with excessive dyskinesia, irritability and reflux, or they have incomplete or inadequate response with regard to their motor manifestations of the disorder [16,17]. When diagnosis occurs late in such patients, motor development must

resume from the current level and slow improvement over months is to be expected, in contrast with the often rapid improvement noted in less severely affected patients in whom early motor developmental milestones were previously achieved.

In contrast with GTPCH deficiency, treatment with L-dopa/carbidopa alone may lead to severe dyskinesias with marked on–off effects in such patients. The addition of dopamine agonists, such as selegiline, or anticholinergic agents, such as trihexyphenidyl, can provide significant benefit and help promote the gradual ongoing attainment of motor skills and the ability to ambulate independently, but such achievements may take years, rather than months or weeks, in the most severely affected patients. While more mildly affected patients may tolerate 1–3 mg/kg/dose of L-dopa, 2–4-times per day, severely affected infants and younger children require L-dopa quantities as low as 0.2 mg/kg/dose. Breaking standard formulations of L-dopa/carbidopa into greater than two doses per tablet is not advisable, since the amount of carbidopa will then be insufficient to help enhance transport of L-dopa across the blood–brain barrier and minimize peripheral side effects such as nausea, reflux, decreased appetite or vomiting. Carbidopa should be maintained at a minimum of approximately 1 mg/kg/dose up to 25 mg/dose, no matter the L-dopa requirement. Slow institution of small, compounded doses of L-dopa/carbidopa, along with selegiline (monoamine oxidase inhibitor [MAO]-B inhibitor) and an anticholinergic agent such as trihexyphenidyl, may be more beneficial than L-dopa/carbidopa alone [18]. Selegiline doses may also require compounding, since low-dose formulations are currently unavailable for use in infants. Frequent side effects of excessive dosing include eating disorders, nightmares and insomnia. Dosing should begin in the range of 0.1 mg/kg and increase as tolerated. Patients with a mild form of the disorder, such as an isolated gait disorder or exercise-associated dystonia, respond well to monotherapy with L-dopa/carbidopa and rarely develop dyskinesias.

Although, to date, inheritance in most families is recessive, at least one family has been described whereby the father of the affected proband had mild exercise-induced dopa-responsive dystonia, raising the possibility that TH deficiency could present in an autosomal dominant fashion in some families with a

milder phenotype [19]. We have observed restless leg syndrome in three women with heterozygous mutations in the *TH* gene, all mothers of affected patients with more classic phenotypes [Swoboda KJ, Unpublished Data]. In two of these individuals, CSF HVA levels were below normal values, but were reduced to a lesser degree than in their affected children. Whether females are more likely to demonstrate a manifest carrier phenotype with heterozygous *TH* mutations requires additional study. To date, an increase in penetrance for motor symptoms in females in families with *TH* deficiency has not been documented clearly, as is evidenced in families with GTPCH; however, the autosomal recessive nature of the disorder, the small number of families described and the lack of large multiplex families would make such an observation more difficult. The mechanisms resulting in gender-dependent predominance of motor features in disorders associated with dopamine deficiency remain poorly understood but are deserving of further study, and may have wider implications in more common disorders such as Parkinson's disease.

Aromatic L-amino acid decarboxylase or dopa-decarboxylase deficiency

Aromatic L-amino acid decarboxylase is a pyridoxine-dependent enzyme that decarboxylates L-dopa and 5-HTP to make dopamine and serotonin, respectively. Patients with this disorder typically present in the first few months of life with dystonia or intermittent limb spasticity, axial and truncal hypotonia, oculogyric crises, autonomic symptoms and ptosis [20]. Neonatal symptoms including feeding difficulties, ptosis, lethargy and hypothermia are common. Neurological signs and symptoms are clearly evident within the first few months of life in all patients reported to date. These patients demonstrate multisystemic involvement with a wide array of neurological difficulties, including problems with sleep, attention, emotional regulation and cognitive function that extend well beyond their motor difficulties. As they become older, gross motor delays with fluctuating tone, ataxia and expressive speech impairment are prominent features, even in the patients with the best outcomes.

The phenomenology of the movement disorder is remarkably similar amongst the cases, and not surprisingly shares a number of features in common with children with BH₄ deficiency

disorders such as 6-pyruvoyltetrahydropterin synthase (PTS) and dihydropteridine reductase (DHPR) deficiency, and the autosomal recessive form of GTPCH deficiency. Intermittent oculogyric crises and limb dystonia, generalized athetosis and an overall paucity of voluntary movement become evident between 1 and 6 months of age. Tongue thrusting, ocular convergence spasm, myoclonic jerks and episodes of sudden loss of head control or episodes resembling flexor spasms are common, and may lead to a clinical diagnosis of epilepsy. Oculogyric crises, orofacial dystonia, torticollis, limb tremor with attempted voluntary movement and blepharospasm are often the most compelling evidence supporting a defect in dopaminergic transmission. Breath holding or apneic spells, paroxysmal sweating, nasal congestion, sudden respiratory or cardiorespiratory arrest, unresponsiveness associated with hypoglycemia, intermittent hypothermia and feeding and gastrointestinal issues are manifestations of the often profound autonomic dysfunction these patients demonstrate [21]. In the rare patients who become ambulatory, gait often appears frankly ataxic rather than predominantly dystonic.

CSF neurotransmitter metabolites show a characteristic pattern with low HVA and 5-HIAA, markedly elevated 3-O-methyldopa, 5-hydroxytryptophan and L-dopa, and normal bipterin and neopterin levels. Plasma L-dopa is markedly elevated. Urine catecholamines may be reduced or elevated [22,23]. Urine organic acid analysis demonstrates elevated vanillic acid as well as vanilpyruvic acid (VPA), N-acetyl-vanilalanine and N-acetyl-tyrosine [24]. While quantities of these compounds are low, such screening can provide clues to the diagnosis, particularly if one alerts the laboratory to a suspected clinical diagnosis. Enzyme assay of plasma AADC confirms the diagnosis. Enzymatic testing is critical, since a potentially treatable disorder caused by pyridoxamine 5'-phosphate oxidase is able to demonstrate a nearly identical CSF neurotransmitter metabolite profile; infants suffering this rare disorder present with a neonatal epileptic encephalopathy, and may demonstrate significant improvements with pyridoxal phosphate treatment [25,26]. Genetic testing for AADC mutations via sequence analysis is now available on a clinical basis and is extremely valuable for genetic counseling purposes and prenatal diagnosis.

Role of tetrahydrobiopterin supplementation in disorders of amine biosynthesis

BH₄ is required for the hydroxylation of aromatic amino acids, and is thus essential for the production of amine neurotransmitters within the CNS. In GTPCH deficiency, CNS BH₄ deficiency is the primary defect leading to the deficiency of the neurotransmitter precursors 5-HTP and L-dopa, required for the synthesis of the neurotransmitters serotonin and dopamine from the amino acids tryptophan and tyrosine. In disorders of amine biosynthesis associated with elevated plasma phenylalanine, a BH₄-dependent process can be strongly suspected when normalization of phenylalanine levels occurs following BH₄ supplementation. A dose of BH₄ 5 mg/kg is usually necessary to correct peripheral hyperphenylalaninemia in these conditions. In autosomal-dominant GTPCH deficiency, current treatment protocols fail to address the primary BH₄ deficiency, since supplementation of the neurotransmitter precursor L-dopa leads to dramatic improvement and often complete amelioration of the more evident movement disorder phenotype. However, this may lead to a failure to ascertain other, often significant, symptoms associated with defects in serotonin production or BH₄ deficiency, such as anxiety or depression, particularly in males in whom a movement disorder is less likely to manifest. Owing to poor blood–brain barrier penetrance, a much higher dose of BH₄ is required for CNS penetration; limited case reports suggest that doses of BH₄ 20 mg/kg may normalize CSF BH₄ levels in some cases, but additional studies are required.

Nitric oxide synthase also has an absolute requirement for BH₄ for the oxidation of arginine to nitric oxide. The inability to replete normal levels of BH₄ in the CNS with oral administration in doses currently used to correct peripheral hyperphenylalaninemia may be one reason why many children with BH₄-deficient disorders develop lifelong cognitive and developmental impairments despite other treatments. Nitric oxide plays a critical role in CNS neuroprotective mechanisms, and reduced efficiency of this enzyme may result in additional ongoing neuronal injury, cell death and vascular dysregulation and injury.

Current treatment approaches

In the large majority of patients with Segawa's syndrome treatment with L-dopa/carbidopa leads to a significant benefit or resolution of

motor symptoms within a few weeks. However, compound heterozygotes or patients with long-standing or more severe motor manifestations, such as Parkinsonism or spastic paraparesis, may require more careful titration of dosing, with gradual adjustment over a period of several months. Mood manifestations, such as depression or anxiety, often respond to L-dopa treatment as well, but some patients have additional benefit from directed treatment of their associated serotonin deficiency, either with the serotonin precursor 5-HTP or a serotonin reuptake inhibitor or other antidepressant medication.

Patients with TH deficiency, in contrast with those with GTPCH deficiency, can be extremely sensitive to the initiation of neurotransmitter precursors. Starting with extremely conservative dosages, increasing the dosage slowly over weeks or months, and ensuring that the peripheral aromatic L-amino acid decarboxylase is fully blocked by providing ample carbidopa can make the transition to treatment easier. In patients with either GTPCH or TH deficiency, the rate or degree to which children respond depends upon a variety of factors, for example age of diagnosis, specific disorder and mutation and associated confounding factors, including central deficiency of BH₄ and other neurotransmitters. In general, optimism regarding improvement is warranted in most cases.

Institution of neurotransmitter precursor treatment may lead to new problems, such as intermittent dyskinesia related to a peak dose effect in the case of TH deficiency, changes in appetite, gastroesophageal reflux, diarrhea or constipation. These problems, greatest in the first few weeks of institution of treatment, tend to improve with time. With regard to replacement of L-dopa, use of a slow release form of the medication may theoretically be ideal. However, such formulations are not designed for use in children but for adults with Parkinson's disease. Dividing standard dosage forms marketed for adults makes adequate dosing in infants and young children a significant challenge. Thus, ideal dosage forms may need to be formulated in compounded preparations, rather than via commercially marketed dosage preparations. Support for parents and children during this often difficult period of transition from the initiation of treatment to the adjustment of medications is critical, as these patients will likely require neurotransmitter precursor replacement throughout their lifetimes.

In children with AADC deficiency, treatment is complex, and these patients are vulnerable to an array of medication-related side effects. Instead of neurotransmitter precursor replacement, as in the BH₄-deficiency related disorders, the use of neurotransmitter receptor agonists or strategies to hinder reuptake or metabolism of endogenously-produced neurotransmitters is necessary. Reported benefit has been noted in a subset of patients with monoamine oxidase inhibitors, dopamine receptor agonists, anticholinergic agents, pyridoxine and, in rare cases, associated with a defect in the *AADC* gene at the dopa-binding site, L-dopa [27]. With regard to direct dopamine receptor agonists, only adult formulations of these often potent medications are available, making the use of compounding necessary. Giving more frequent and lower doses throughout the day may be necessary in some children in order to achieve optimal benefit. However, in spite of a variety of treatment interventions directed at ameliorating the effects of the associated neurotransmitter deficiency state, overall clinical outcomes remain poor. To date, all patients have had some degree of cognitive impairment, and there is increasing evidence of a gender-dependent discrepancy in severity, with females demonstrating the most severe phenotypes [28].

Conclusions

Disorders of amine biosynthesis present with a wide range of neurological and psychiatric phenotypes, which are not limited to their signature movement disorders. Diagnosis and treatment of these conditions is often rewarding, but with the more severe defects, also presents significant challenges. These rare inborn errors of neurotransmitter synthesis provide us with valuable tools to help increase our understanding of the role of amines in neurological development and can provide insights in helping us to dissect the complex interactions of these and other pathways as they contribute to the regulation of movement, activity levels, mood, attention, motivation and sleep. The phenomenology of the associated movement disorders in these syndromes offer insights into the diurnal variation of neurotransmitter function and the increased penetrance of mutations with age in association with age-related declines in neurotransmitter biosynthesis, as seen in GTPCH deficiency. The evolution of the movement disorder over the first few months of life in AADC deficiency offers insights into the effects of developmental status on the manifestation of a given movement disorder phenotype. Finally, these disorders highlight gender-related

differences in responses to neurotransmitter deficiency states, which may have wider implications for related neurological conditions.

Future perspective

With more widespread testing of CSF neurotransmitter metabolites, patients are being identified with documented neurotransmitter deficiency states in which an evident enzyme deficiency or gene defect cannot be readily identified. These include patients with a wide variety of movement disorder phenotypes, encephalopathy and seizures. Additional studies are required to determine the precise defects affecting neurotransmitter levels and to ascertain whether they are primary or secondary. These as yet undefined neurotransmitter deficiency states provide the opportunity for the identification of novel disorders of the aminergic pathways or receptors. In addition, CSF neurotransmitter metabolite and pterin assays provide a valuable tool to improve the characterization of patients with already defined clinical disorders, such as parkinsonism syndromes. Such patients may benefit from directed treatment approaches targeted to other neurotransmitter deficiency states, which may accompany their primary defect, or to their associated CNS BH₄ deficiency if present. Furthermore, CSF biochemical profiling provides additional opportunities to gain new insights on disorders about which we already know a great deal, such as Parkinson's disease. While the treatment outcomes in patients with a classic dopa-responsive dystonia syndrome are considered relatively good, these disorders still have much to teach us as we look beyond the movement disorder phenotypes. More basic research to help improve our understanding of why dyskinesias are the rule in TH deficiency, but a rarity in GTPCH deficiency, could lead to important insights and altered treatment approaches for the dyskinesias observed in the latter stages of Parkinson's disease. Further significant progress in treatment outcomes in disorders such as AADC deficiency, where the replacement of neurotransmitter precursors is ineffective, will likely require aggressive approaches early in infancy, such as stem cell therapy or direct CSF delivery of enzyme or neurotransmitters. Investigators working on AADC enzyme replacement as a means of treating Parkinson's disease should take a closer look at this population as a unique opportunity to better understand the critical role of this enzyme in neurological function and development.

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Executive summary

- Inherited disorders of amine biosynthesis result in variable deficiency states of the indoleamine and catecholamine neurotransmitters serotonin, dopamine, norepinephrine and epinephrine.
- These disorders are comprised of two groups: those with elevated plasma phenylalanine and those with normal phenylalanine levels. Those in the first group are usually identified via newborn screening; the latter are most frequently identified later in childhood, in the context of an associated movement disorder.
- Aromatic L-amino acid decarboxylase (AADC), guanine triphosphate cyclohydrolase (GTPCH) and tyrosine hydroxylase (TH) deficiencies are linked by their shared dopamine deficiency states, but their diverse patterns of inheritance, phenomenology of the movement disorder and variable responses to treatment provide a unique opportunity to help us improve our understanding of the complex role of dopamine in neurodevelopmental processes.
- An increasingly broad range of symptoms is recognized in affected individuals and carriers of these disorders, including abnormalities of mood, attention mechanisms, cognition and sleep, often in the absence of the characteristic movement disorder.
- Gender clearly modifies phenotype in GTPCH deficiency, with increased penetrance of motor phenotypes in females. Girls also appear to be more severely affected in AADC deficiency. The broader implications for gender effects in other dopamine deficiency states may have significant implications for disorders such as Parkinson's disease, and deserve further study.
- Therapeutic targeting via the use of the neurotransmitter precursor L-dopa has been tremendously effective in treating the associated movement disorder phenotypes in GTPCH and TH deficiency; however, the importance of addressing the associated serotonin deficiency and its implications for associated mood and behavioral disorders in GTPCH is under-recognized.
- The importance of tetrahydrobiopterin (BH4) within the CNS is currently underestimated; its potential role in treating more severely affected patients with GTPCH activity and other amine biosynthetic defects with suboptimal clinical outcomes deserves further study.
- Treatment of AADC deficiency via the use of direct receptor agonists, anticholinergic agents and monoamine oxidase or catechol-O-methyl transferase inhibitors may ameliorate symptoms in some cases, but outcomes remain suboptimal in the majority of reported cases. More aggressive treatment approaches early in infancy, such as stem cell therapy or cerebrospinal fluid infusion of neurotransmitters, will likely prove necessary to achieve further improvement in outcomes.

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Website

101. GeneTests website. www.genetests.org

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