The monoamine neurotransmitter disorders: an expanding range of neurological syndromes

Manju A Kurian, Paul Gissen, Martin Smith , Simon J R Heales, Peter T Clayton

The monoamine neurotransmitter disorders consist of a rapidly expanding heterogeneous group of neurological syndromes characterised by primary and secondary defects in the biosynthesis, degradation, or transport of dopamine, norepinephrine, epinephrine, and serotonin. Disease onset can occur any time from infancy onwards. Clinical presentation depends on the pattern and severity of neurotransmitter abnormalities, and is predominated by neurological features (encephalopathy, epilepsy, and pyramidal and extrapyramidal motor disorders) that are primarily attributed to deficiency of cerebral dopamine, serotonin, or both. Many neurotransmitter disorders mimic the phenotype of other neurological disorders (eg, cerebral palsy, hypoxic ischaemic encephalopathy, paroxysmal disorders, inherited metabolic diseases, and genetic dystonic or parkinsonian syndromes) and are, therefore, frequently misdiagnosed. Early clinical suspicion and appropriate investigations, including analysis of neurotransmitters in CSF, are essential for accurate clinical diagnosis. Treatment strategies focus on the correction of monoamine deficiency by replacement of monoamine precursors, the use of monoamine analogues, inhibition of monoamine degradation, and addition of enzyme cofactors to promote monoamine production.

Introduction

Brain neurotransmission is an essential process for neuronal differentiation and growth, as well as for the development of interneuronal communication and neuronal circuitry.[1] Inherited abnormalities in neurotransmitter synthesis, breakdown, and transport represent an expanding group of neurometabolic syndromes with important therapeutic implications.[2] Symptoms are determined by the type and severity of the disorder and are dominated by neurological features, including developmental delay, pyramidal and extrapyramidal motor disorders, epilepsy, autonomic dysfunction, and neuropsychiatric symptoms. Overall, the clinical phenotype mimics that of many other neurological disorders and, therefore, misdiagnosis or diagnostic delay are common. Onset can occur at any age but is most frequently in infancy or early childhood.

Neurotransmitter disorders are due to aberrant metabolism or transport of the biogenic amines, glycine, vitamin B6, GABA, and glutamic acid.[2–4] The biogenic amines are a functionally important group of brain neurotransmitters[5] and consist of the catecholamines (dopamine, norepinephrine, and epinephrine) and serotonin. Dopamine and serotonin have key roles in the brain, including the control of locomotion, mood, and behaviour.

In this Review, we focus on the monoamine neurotransmitter disorders that lead to depletion in availability of dopamine, serotonin, or both. We aim to clearly define the clinical, biochemical, and molecular genetic features of disorders of pterin, dopamine, and serotonin metabolism (figure 1, table). A practical guide to specialist diagnostic investigations and a comprehensive therapeutic approach to each monoamine neurotransmitter disorder will also be discussed.

Role of dopamine and serotonin

Metabolism of dopamine and serotonin in the brain are postulated to be closely linked at biochemical and physiological levels (figure 2).[8,9] Dopamine was thought to be a purely intermediary substrate in the biosynthesis of norepinephrine and epinephrine, until the 1950s, when Carlsson and colleagues[10] discovered that dopamine was present in high concentrations in the rat corpus striatum. Administration of reserpine, which blocked the vesicular monoamine transporter, led to dopamine depletion and parkinsonism that were reversible with use of levodopa. Carlsson[11] thus proposed an independent biological role for dopamine in neurotransmission. Mapping studies showed dopaminergic cell bodies in the ventral midbrain and widespread distribution in the striatum.[12] This finding led to the hypothesis that dopamine is involved in control of motor function and that decreased striatal concentrations could cause extrapyramidal disorders, such as Parkinson's disease. Later mapping studies[13–15] showed that dopamine has a much wider distribution outside the basal ganglia, which suggests a more complex, extended role in the brain. Dopaminergic neurons are located mainly in the substantia nigra pars compacta (with projections to the striatum via the nigrostriatal pathway), ventral tegmental area of the midbrain (with mesocorticolimbic projections to the nucleus accumbens, hippocampus, and other corticolimbic structures), and the hypothalamus (with projections to the pituitary gland via the tuberoinfundibular pathway).[16] Various important physiological functions, such as control of voluntary locomotion, cognitive processes (including attention and memory), neuroendocrine secretion (prolactin), and control of motivated behaviours, such as emotion, affect, and reward mechanisms, therefore, have been attributed to dopamine.[17–19]

Serotonergic neurons principally arise from the midbrain dorsal and ventral raphe nuclei, which are centred on the reticular formation, with widespread projections to several supratentorial cortical areas—the supplementary motor area, premotor cortex, and primary motor cortex—and infratentorially to the cerebellum and spinal cord.[20–22]
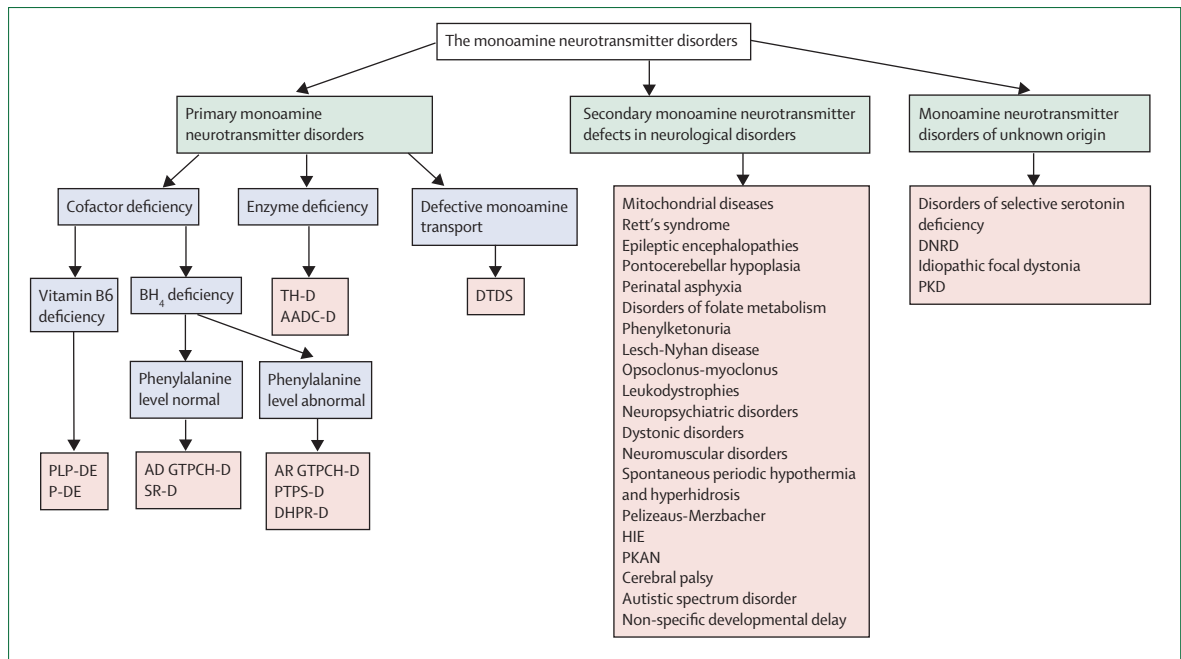
Figure 1: Classification of the monoamine neurotransmitter disorders

BH$_4$=tetrahydrobiopterin. TH-D=tyrosine hydroxylase deficiency. AADC-D=aromatic L-aminoacid decarboxylase deficiency. DTDS=dopamine transporter deficiency syndrome. PLP-DE=pyridoxal-phosphate-dependent epilepsy. P-DE=pyridoxine-dependent epilepsy. AD GTPCH-D=autosomal dominant GTP cyclohydrolase 1 deficiency. SR-D=sepiapterin reductase deficiency. AR GTPCH-D=autosomal recessive GTP cyclohydrolase 1 deficiency. PTPS-D=6-pyruvoyltetrahydropterin synthase deficiency. DHPR-D=dihydropteridine reductase deficiency. HIE=hypoxic ischaemic encephalopathy. PKAN=pantothenate kinase associated neurodegeneration. DNRD=dopa non-responsive dystonia. PKD=paroxysmal kinesogenic dyskinesia.

Serotonergic innervation of the basal ganglia is sparse in the caudate nucleus, moderate in the putamen, substantia nigra, and ventral tegmental area, and dense in the globus pallidus.[23] This innervation pattern implicates a role for serotonin in motor control, and is supported by diminished serotoninergic motor responses and increased sensitivity to serotoninergic agonists in genetically dystonic rats.[24] In human beings, serotonin syndrome, which has major motor features, including dystonia, arises from iatrogenic increases of synaptic serotonin or stimulation of serotoninergic receptors.[25] Serotonin is also thought to play a part in autonomic control of respiration and temperature and in mood.[26]

Hoffmann and colleagues[27] have attempted to separate the effects of dopamine and serotonin deficiency. Proposed signs of dopamine deficiency include parkinsonism, dystonia, chorea, oculogyric crises, ptosis, hypersalivation, and myoclonic epilepsy. Non-specific symptoms include

	Age at presentation	Motor and cognitive delay	Extrapyramidal hyperkinetic features	Extrapyramidal hypokinetic features	Pyramidal tract features	Epilepsy	Autonomic features	Neuropsychiatric features
AD GTPCH-D	Childhood (but can occur at any age)	Not common	Yes	Yes	No	No	No	Yes
SR-D	Infancy	In most	Yes	Yes	Yes	Yes	Yes	Yes
AR GTPCH-D	Infancy	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PTPS-D	Infancy to childhood	In most	Yes	Yes	Yes	Yes	Yes	Yes
DHPR-D	Infancy to childhood	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PCD-D	Infancy	No	No	No	No	No	No	No
TH-D	Infancy to early childhood	In most	Yes	Yes	Yes	Yes	Yes	No
AADC-D	Mainly infancy (but can occur at any age)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PLP-DE	Infancy to early childhood	In most	Yes	Yes	Yes	Yes	Yes	Yes
DTDS	Infancy	Yes	Yes	Yes	Yes in older children	No	Yes	No

Infancy is age <1 year and childhood 1–10 years. AD GTPCH-D=autosomal dominant GTP cyclohydrolase 1 deficiency. SR-D=sepiapterin reductase deficiency. AR GTPCH-D=autosomal recessive GTP cyclohydrolase 1 deficiency. DHPR-D=dihydropteridine reductase deficiency. PTPS-D=6-pyruvoyltetrahydropterin synthase deficiency. PCD-D=pterin-4α-carbinolamine dehydratase deficiency. TH-D=tyrosine hydroxylase deficiency. AADC-D=aromatic L-aminoacid decarboxylase deficiency. PLP-DE=pyridoxal-phosphate-dependent epilepsy. DTDS=dopamine transporter deficiency syndrome.

Table: Clinical features of the monoamine neurotransmitter disorders

epileptic encephalopathy, progressive cognitive dysfunction, microcephaly, swallowing difficulties, and pyramidal tract features. The manifestations of serotonin deficiency are less well defined, but include temperature instability, sweating, and possibly dystonia.

Neurological investigations

The diagnosis of a monoamine neurotransmitter disorder is established on the basis of clinical history, physical examination, biochemical investigations, enzyme analysis (for some disorders), and analysis of genetic mutations (figure 3).[28] The specific pattern of neurotransmitter metabolites can be indicative of a particular neurotransmitter disorder (figure 3).

Neurotransmitter concentrations in CSF

CSF for neurotransmitter analysis is obtained by lumbar puncture. Concentrations of the amine neurotransmitter metabolites homovanillic acid (HVA) and 5-hydroxy-indoleacetic acid (5-HIAA), which are the stable degradation products of dopamine and serotonin, respectively, reflect turnover of these biogenic amines in the mesolimbic and mesostriatal areas of the brain.[28–30] Concentrations of individual pterin species (eg, tetra-hydrobiopterin [BH_4], neopterin, and biopterin) and folate should also be measured.

Neurotransmitter analysis in CSF must be done by a specialist neurometabolic laboratory that has strict protocols for sample collection and test interpretation.[2,31] Samples must be snap frozen in liquid nitrogen or dry ice because BH_4 in CSF is labile.[32] Individual pterin species require special preservatives in the sample collection tubes. Red blood cells in the CSF lead to rapid oxidation of neurotransmitter metabolites and blood-contaminated samples must be centrifuged immediately, after which clear CSF should be transferred to new tubes before freezing. CSF samples must be stored at –80°C until analysis. Diurnal variation can affect metabolite levels and, therefore, the time of collection should be recorded. High-pressure liquid chromatography with electrochemical detection and reversed phase column is the most widely used method.[28] The rostrocaudal gradient of neurotransmitter metabolites and BH_4 requires that the same fractions of CSF are used for all metabolite analyses and that results are compared with established age-matched reference ranges.[9] Concentrations of dopamine and serotonin metabolites are high at birth but decrease rapidly within the first few months of life then more slowly into adulthood.[11] High concentrations of HVA and 5-HIAA in infants are thought to be required for the regulation of the metabolic pathways during mitosis, neurogenesis, migration, and formation of dopaminergic neuron networks.[28]

Blood and urine measurements

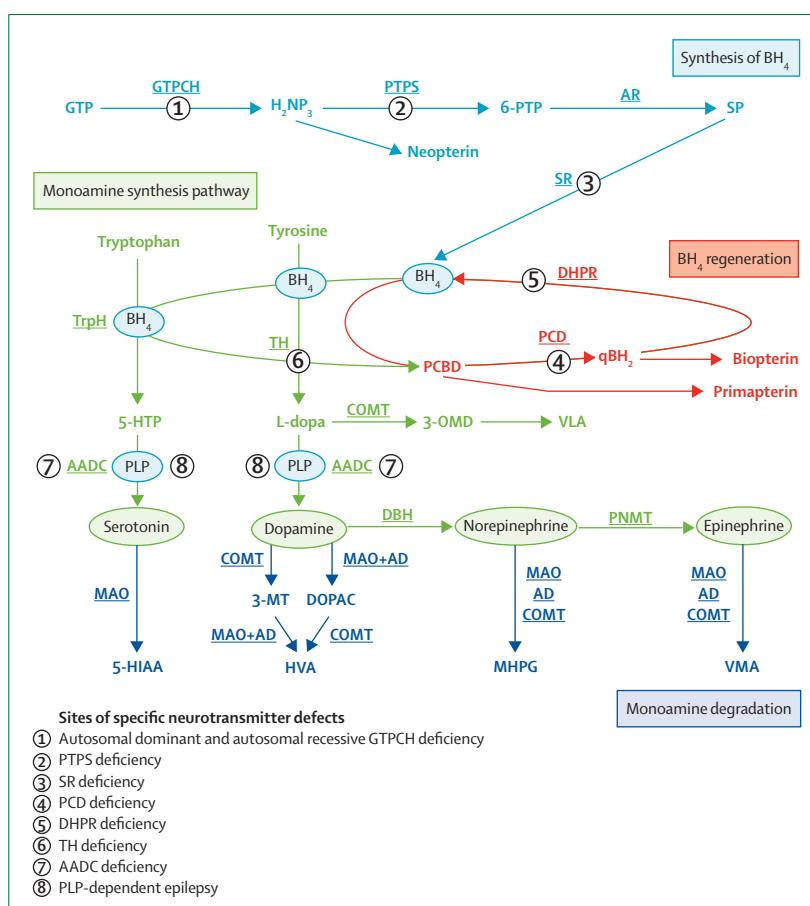Analysis of specific pterins and biogenic amine metabolites in blood and urine can aid diagnosis when assessed in

Figure 2: **The monoamine neurotransmitter biosynthesis pathway**

BH_4 is synthesised in four enzymatic steps from GTP. BH_4 is a necessary cofactor for TrpH and TH, the rate limiting enzymes in monoamine synthesis. Tryptophan is converted to 5-HTP by TrpH. Tyrosine is converted to L-dopa by TH. The conversion of 5-HTP to serotonin and of L-dopa to dopamine is catalysed by AADC and its cofactor PLP. When BH_4 acts as a cofactor for TH and TrpH, it is converted to PCBD, which in turn is converted to BH_4 (in the BH_4 regeneration pathway) by a two-step process involving PCD and DHPR. After synthesis, uptake of monoamine neurotransmitters into the synaptic secretory vesicles requires the vesicular monoamine transporter VMAT (not shown).[6] After synaptic transmission, serotonin and dopamine are metabolised through similar pathways, which involve MAO enzymes and COMT. Presynaptic reuptake of the monoamines is facilitated by DAT and SERT (not shown).[7] Metabolic pathway of BH_4 synthesis is shown in light blue, monoamine synthesis in light green, monoamine catabolism in dark blue, and BH_4 regeneration in red. The biogenic amines are illustrated in light green circles and the cofactors (BH_4 and PLP) are represented by light blue circles. Enzymes in the monoamine neurotransmitter pathway are underlined. GTPCH=GTP cyclohydrolase 1. H_2NP_3=dihydroneopterin triphosphate. PTPS=6-pyruvoyltetrahydropterin synthase. 6-PTP=6-pyruvoyltetrahydropterin. AR=aldose reductase. SP=sepiapterin. SR=sepiapterin reductase. BH_4=tetrahydrobiopterin. TrpH=tryptophan hydroxylase. TH=tyrosine hydroxylase. DHPR=dihydropteridine reductase. PCBD=tetrahydrobiopterin-α-carbinolamine. PCD=pterin-4α-carbinolamine dehydratase. qBH_2=(quinonoid) dihydrobiopterin. 5-HTP=5-hydroxytryptophan. L-dopa=levodihydroxyphenylalanine. COMT=catechol-O-methyltransferase. 3-OMD=3-ortho-methyldopa. VLA=vanillactic acid. AADC=aromatic L-amino acid decarboxylase. PLP=pyridoxal phosphate. DBH=dopamine β hydroxylase. PNMT=phenylethanolamine N-methyltransferase. MAO=monoamine oxidase. AD=aldehyde dehydrogenase. 3-MT=3-methoxytyramine. DOPAC=3,4-dihydroxyphenylacetic acid. 5-HIAA=5-hydroxyindoleacetic acid. HVA=homovanillic acid. MHPG=3-methoxy-4-hydroxylphenylglycol. VMA=vanillylmandelic acid.

conjunction with clinical findings and CSF neurotransmitter studies.[33,34] In urine, measurement of pterins, including biopterin and neopterin, can indicate specific metabolic defects, such as deficiencies in GTP cyclohydrolase 1 (GTPCH), pyruvoyl-tetrahydropterin synthase (PTPS), dihydropteridine reductase (DHPR), and sepiapterin reductase (SR). Concentrations of
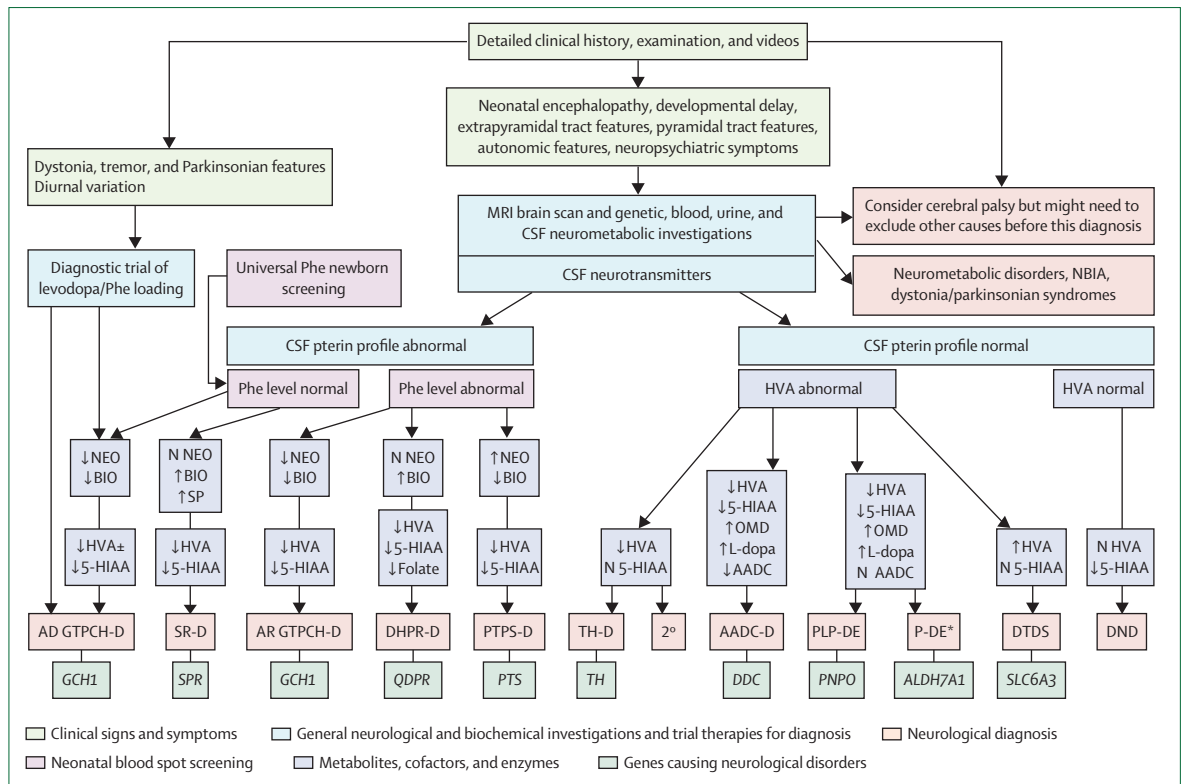
Detailed clinical history, examination, and videos

Neonatal encephalopathy, developmental delay, extrapyramidal tract features, pyramidal tract features, autonomic features, neuropsychiatric symptoms

Dystonia, tremor, and Parkinsonian features. Diurnal variation

MRI brain scan and genetic, blood, urine, and CSF neurometabolic investigations

Consider cerebral palsy but might need to exclude other causes before this diagnosis

CSF neurotransmitters

Neurometabolic disorders, NBIA, dystonia/parkinsonian syndromes

Diagnostic trial of levodopa/Phe loading

Universal Phe newborn screening

CSF pterin profile abnormal

CSF pterin profile normal

Phe level normal — Phe level abnormal

HVA abnormal — HVA normal

↓NEO ↓BIO → ↓HVA± ↓5-HIAA → AD GTPCH-D → GCH1

N NEO ↑BIO ↑SP → ↓HVA ↓5-HIAA → SR-D → SPR

↓NEO ↓BIO → ↓HVA ↓5-HIAA → AR GTPCH-D → GCH1

N NEO ↑BIO → ↓HVA ↓5-HIAA ↓Folate → DHPR-D → QDPR

↑NEO ↓BIO → ↓HVA ↓5-HIAA → PTPS-D → PTS

↓HVA N 5-HIAA → TH-D → TH

2°

↓HVA ↓5-HIAA ↑OMD ↑L-dopa ↓AADC → AADC-D → DDC

↓HVA ↓5-HIAA ↑OMD ↑L-dopa N AADC → PLP-DE → PNPO

P-DE* → ALDH7A1

↑HVA N 5-HIAA → DTDS → SLC6A3

N HVA ↓5-HIAA → DND

Legend:
- Clinical signs and symptoms
- General neurological and biochemical investigations and trial therapies for diagnosis
- Neurological diagnosis
- Neonatal blood spot screening
- Metabolites, cofactors, and enzymes
- Genes causing neurological disorders

Figure 3: **Algorithm for the investigation and diagnosis of monoamine neurotransmitter disorders based on clinical presentation**
Appropriate neurometabolic investigations in blood, urine, and CSF could include the following: in blood, measurement of glucose, lactate, ammonia, aminoacids, biotinidase, thyroid function tests, acylcarnitine, carnitine profile, white-cell enzymes, and very-long-chain fatty acids; in urine, measurement of aminoacids, organic acids, oligosaccharides, purines, and pyrimidines; in CSF, measurement of glucose, lactate, aminoacids, and neurotransmitter profile. Skin and muscle biopsy may be undertaken for specialist metabolic investigations. NBIA=neurodegeneration with brain iron accumulation. Phe=phenylalanine. HVA=homovanillic acid. NEO=neopterin. BIO=biopterin. N=normal. SP=sepiapterin. 5-HIAA=5-hydroxyindoleacetic acid. OMD=3-ortho-methyldopa. L-dopa=levodihydroxyphenylalanine. AADC=aromatic L-amino acid decarboxylase. AD GTPCH-D=autosomal dominant GTP cyclohydrolase 1 deficiency. SR-D=sepiapterin reductase deficiency. AR GTPCH-D=autosomal recessive GTP cyclohydrolase 1 deficiency. DHPR-D=dihydropteridine reductase deficiency. PTPS-D=6-pyruvoyltetrahydropterin synthase deficiency. TH-D=tyrosine hydroxylase deficiency. 2°=secondary monoamine neurotransmitter defects. AADC-D=aromatic L-aminoacid decarboxylase deficiency. PLP-DE=pyridoxal-phosphate-dependent epilepsy. P-DE=pyridoxine-dependent epilepsy. DTDS=dopamine transporter deficiency syndrome. DND=dopa non-responsive dystonia. *Measurement of urine α-aminoadipic semialdehyde can assist diagnosis and differentiation of P-DE from PLP-DE.

3-ortho-methyldopa and vanillactic acid are raised in aromatic-L-aminoacid decarboxylase (AADC) deficiency. In dopamine transporter deficiency syndrome (DTDS) the ratio of urinary HVA to creatine is raised.

The universal neonatal Guthrie blood spot screen and plasma aminoacid analysis can be used to detect hyperphenylalaninaemia associated with certain pterin metabolism defects. Prolactin release is suppressed by dopamine and, therefore, a high concentration of prolactin in serum, especially when accompanied by galactorrhoea,[35] might indicate dopamine deficiency.

Enzyme activity

Measurement of residual enzyme activity is not routinely undertaken for most monoamine neurotransmitter disorders secondary to enzymatic defects, and molecular genetic studies are generally preferred. Enzyme analysis can be useful, however, to assess features such as GTPCH activity in fibroblasts in patients with suspected autosomal dominant GTPCH deficiency, particularly if the CSF neurotransmitter profile is atypical and *GCH1* screening is negative. SR activity in fibroblasts can be measured to confirm SR deficiency. Measurements of DHPR in blood spots and AADC in plasma can help to diagnose deficiencies in these enzymes.

Phenylalanine load test

In disorders of biopterin metabolism without hyperphenylalaninaemia an oral phenylalanine load test can be useful.[36,37] A raised ratio of phenylalanine to tyrosine in serum after oral phenylalanine loading suggests a defect in BH_4 metabolism. Measurements are usually taken at 1, 2, 4, and 6 h, but one measurement 2–4 h after ingestion could be sufficient for diagnosis, especially if accompanied by a decline in biopterin concentration. Normalisation of serum tyrosine concentration after phenylalanine load combined with BH_4 supplementation indicates a BH_4 defect. The potential for false-negative results in patients with true GTPCH deficiency[38] and false-positive results in carriers of *PAH* mutations

associated with phenylketonuria[39] means that results must be interpreted with caution, in the context of results from clinical, biochemical, and molecular genetic investigations, and in comparison with appropriate age-matched reference values.[37]

Molecular genetics

Analysis of mutations in specific genes can be undertaken for diagnostic confirmation of monoamine neurotransmitter disorders.

Primary monoamine neurotransmitter disorders
Pterin metabolism defects without hyperphenylalaninaemia
Autosomal dominant GTPCH deficiency

Autosomal dominant GTPCH deficiency (Online Mendelian Inheritance in Man mutation number [OMIM] #128230; also known as Segawa disease, DYT 5a, and dopa-responsive dystonia) was first clinically reported in the 1970s. Segawa and colleagues[40,41] described a syndrome of extrapyramidal basal ganglia features with a striking response to levodopa and, in one adult with a 43-year clinical course, hereditary progressive dystonia with notable diurnal fluctuation.[41]

Age of disease onset is generally around 6 years, but many cases of adult-onset disease are also described.[42–44] This disorder has a strong female preponderance. Onset in childhood is characterised by postural dystonia of the lower limbs, mostly with talipes equinovarus, and some cases also have dystonic posturing of the upper limbs. Action dystonia is also reported but seems to have a later onset than postural dystonia (about 8 years), and sometimes manifests as retrocollis or oculogyric crises. Upper-limb postural tremor (frequency 8–10 Hz in children and lower in adults) might present after around age 10 years. Adult patients mostly present with tremor in the hands, writer's cramp, and gait disturbances. Wider phenotypic features, recognised through improved biochemical and molecular genetic diagnostic techniques,[45] include torticollis, scoliosis, pes cavus, parkinsonism, and paroxysmal exercise-induced dyskinesia.[42–46]

In many patients, movement disorders are asymmetrical. Dystonia and tremor frequently have diurnal fluctuations, especially in children, being more severe towards evening, and are notably improved after rest.[44] Mobility and cognitive function are generally retained, although López-Laso and colleagues[47] have shown borderline mild mental retardation and increased impulsivity in some patients. They reported no depression, anxiety, or obsessive-compulsive disorder, but these and other neuropsychiatric disorders (eg, mood swings, autistic features, and sleep disturbance) have been reported elsewhere.[42,45,48,49] Onset of GTPCH deficiency before adolescence is associated with short stature.[42] Childhood onset of autosomal dominant GTPCH deficiency can strongly mimic diplegic cerebral palsy. Other disorders that need to be ruled out clinically are hereditary spastic paraparesis, juvenile parkinsonism, idiopathic torsion dystonia, and other inherited dystonia syndromes.[42–44]

Response to a trial of combined levodopa and carbidopa (introduced at a low dose and gradually increased to a standard treatment dose of 2–5 mg/kg levodopa daily)[42–44] helps to make the diagnosis. Analysis of neurotransmitters in CSF should also be done, as reduced concentrations of biopterin, neopterin, and HVA in CSF are characteristic of this disorder.[42–44] If a patient is already receiving combined levodopa and carbidopa, treatment must be tapered to a complete stop 3–7 days before lumbar puncture to enable accurate CSF analysis. Compared with activity in healthy individuals, GTPCH activity in mononuclear blood cells in symptomatic patients is less than 20%, and is 30–40% less in asymptomatic patients.[42] A phenylalanine load test is frequently positive. Polysomnography should reveal a decrease in the number of gross and twitch movements in the phasic motor components of sleep.[42] Neuroimaging results are generally normal.

Autosomal dominant GTPCH deficiency is caused by heterozygous mutations in *GCH1* (OMIM *600225) on chromosome 14q22.1–q.22.2. Reported disease penetrance varies.[42–44] Direct gene sequencing methods have detected more than 100 mutations, which are thought to constitute about 60% of all mutations.[50] Promoter-site mutations, intronic changes, and heterozygous deletions or duplications[51,52] that are not detected by conventional mutational screening probably account for at least some of the remaining cases. Patients without recognised mutations might have other as yet undetermined genetic causes or other secondary neurotransmitter defects.

GTPCH has a rate-limiting role in BH_4 synthesis (figure 2).[33] In autosomal GTPCH deficiency the mutant protein encoded by the abnormal allele binds the normal protein encoded by the normal allele, thereby altering its function (known as a dominant negative effect).[42,50] The fractional loss of GTPCH activity in mononuclear cells and rates of mutant *GCH1* messenger RNA production are substantially higher in affected heterozygotes than in asymptomatic carriers.[42] The resulting partial deficiency in BH_4 preferentially affects tyrosine hydroxylase, more than tryptophan hydroxylase, because of its higher affinity for BH_4.[44] Thus, in most cases, clinical symptoms related to dopamine deficiency dominate. In cases in which BH_4 production is greatly reduced, tryptophan hydroxylase is also affected and might lead to symptoms related to serotonin deficiency. Reasons for the female preponderance in GTPCH are unclear, but could be due to genetically determined differences in dopamine neurons.[42]

Treatment with 2–5 mg/kg levodopa daily in a levodopa and carbidopa combined preparation yields an excellent clinical response in most patients.[42–44] Side-effects are rare but treatment should be initiated at low doses and increased gradually to avoid dyskinesia. Full resolution of symptoms is frequently not seen in patients with

action dystonia, and motor symptoms in these patients might even be aggravated.[42] A few affected patients need supplementary therapeutic strategies for symptom control. The addition of BH_4 has been used in some patients, although BH_4 monotherapy is generally not advocated.[42] Anticholinergic agents have been effective adjuvants in the management of dystonia but not tremor.[42]

SR deficiency

Onset of SR deficiency (OMIM #612716) is seen mostly in the first decade of life, and presenting signs and symptoms are features of psychomotor retardation, dystonia, oculogyric crises, choreoathetosis, hypotonia, spasticity, tremor, ataxia, parkinsonism, seizures, temperature instability, hypersalivation, microcephaly, and irritability.[6] Most symptoms show diurnal variation. Psychiatric symptoms of aggression, depression, and hypersomnolence are also reported. Patients with a mild, almost asymptomatic, motor phenotype have been described.[53,54]

Although baseline plasma phenylalanine levels are normal, phenylalanine load test results are frequently positive. In CSF, concentrations of biopterin and SR are raised,[55] concentrations of dihydrobiopterin, HVA, and 5-HIAA are reduced, and that of neopterin is normal.[33,55] Levels of prolactin in serum might be raised. Urine pterin concentrations are generally normal. Measurement of fibroblast SR activity can confirm deficiency.

SR deficiency is caused by loss-of-function mutations in *SPR* (OMIM *182125).[50] Arrabal and colleagues[53] have shown some genotype–phenotype correlations. Patients with the classic severe phenotype had mutations that resulted in null SR function, but patients with a very mild phenotype had an *SPR* splicing defect that resulted in a missense mutation and some residual SR activity.

SR is involved in the NADPH-dependent reduction of carbonyl derivatives in the final stage of BH_4 synthesis (figure 2), and deficiency leads to reductions in dopamine and serotonin biosynthesis.[33] Hyperphenylalaninaemia is not seen because other enzymes (eg, aldose, carbonyl, and dihydrofolate reductase) in peripheral tissues, such as the kidneys and liver, maintain sufficient BH_4 concentrations for adequate phenylalanine hydroxylase activity.[33,50]

Dietary phenylalanine restriction is not required. Supplementation with BH_4, combined levodopa and carbidopa, and 5-hydroxytryptophan is the usual treatment for SR deficiency, and the response is frequently good.[33]

Pterin metabolism defects with hyperphenylalaninaemia
Autosomal recessive GTPCH deficiency

Onset of autosomal recessive GTPCH deficiency (OMIM #233910) is during infancy, and generally presents with developmental delay, pyramidal tract features, dystonia, athetosis, tremor, seizures, and autonomic dysfunction.[33]

This disorder clinically mimics several neurological disorders, including other neurotransmitter defects, alternating hemiplegia of childhood, metabolic disorders, and cerebral palsy. Most patients are identified by the presence of hyperphenylalaninaemia in neonatal blood spot screening.[56,57] Biopterin and neopterin concentrations in urine are low, as are concentrations of HVA, 5-HIAA, and pterins in CSF.[33] Measurement of enzyme activity can be helpful to confirm the diagnosis.

Patients have homozygous or compound heterozygous mutations in *GCH1* (OMIM *600225). Autosomal recessive GTPCH deficiency accounts for less than 10% of cases of GTPCH deficiency (>90% of cases are caused by autosomal dominant GTPCH deficiency).[50] BH_4 synthesis is greatly reduced, which leads to dopamine and serotonin deficiency.

Supplementation of BH_4 is necessary for treatment. Doses of 1–10 mg/kg daily raise phenylalanine hydroxylase activity in the liver, which results in normalisation of phenylalanine levels. The amount of BH_4 entering the brain is not sufficient to sustain appropriate synthesis of neurotransmitters. Precursors of the monoamines (levodopa and 5-hydroxytryptophan) and monoamine oxidase inhibitors (eg, selegiline, tranylcypromine, and moclobemide) are, therefore, also frequently required.[33]

PTPS deficiency

PTPS deficiency (OMIM #261640) is the most frequently seen disorder of BH_4 metabolism.[33,58,59] Patients are classified as having mild and peripheral or severe and generalised disease on the basis, respectively, of normal (<20% of clinical cases) or abnormally low (>80% of clinical cases) concentrations of HVA and 5-HIAA in CSF. Most patients with mild disease have a normal neurological course and excellent prognosis. Severe phenotypes, however, are associated with neurological impairment (dystonia, athetosis, hypotonia, hypokinesia, rigidity, tremor, oculogyric crises, seizures, irritability, and developmental delay) in early infancy, as well as premature birth and low birthweight. Some patients with severe phenotypes also develop neuropsychiatric features, such as obsessive-compulsive disorder, panic attacks, and depression.

Hyperphenylalaninaemia is frequently found in neonatal blood spot screening. In urine, biopterin concentrations are reduced and those of neopterin are increased.[33] In CSF, neopterin concentration is high, but levels of other pterin metabolites, HVA, and 5-HIAA are low. Prolactin concentrations in serum might be raised.

PTPS deficiency is caused by mutations in *PTS* (OMIM *612719) on chromosome 11q22.3–q23.3. More than 50 mutations have been described, with high allelic heterogeneity.[50] Asn52Ser and Pro87Ser are most frequent in Asian populations. Good genotype–phenotype correlations are apparent: specific mutations seem to cause mild phenotypes that are associated with high residual enzyme activity. The severe phenotype seems to arise from genetic mutations that cause a nucleotide frameshift (and subsequent major alterations in coding

sequence) or altered protein zinc binding or oligomerisation.[59] Loss of PTPS activity substantially lessens BH_4 synthesis and leads to impairment of dopamine and serotonin production (figure 2).

Treatment strategies are similar to those for autosomal recessive GTPCH deficiency. In patients with severe disease, outcomes are thought to be improved by early treatment (within 1 month of diagnosis).[58] Brasil and colleagues[60] have shown proof of concept for use of pseudoexon-exclusion therapy with antisense morpholino oligonucleotides in cell lines from three PTPS-deficient patients with intronic mutations resulting in splicing defects. Transcriptional profiling (24 h after transfection) revealed dose-specific and sequence-specific recovery of normal splicing. PTPS enzyme activity in fibroblasts from all three patients and the pterin profiles were close to normal after treatment.

DHPR deficiency

The natural course of DHPR deficiency (OMIM #261630) is thought to be more severe than that of other disorders of pterin metabolism.[33,61] Onset is in the neonatal period or early infancy and is associated with feeding difficulties, bulbar dysfunction, hypersalivation, and microcephaly. Patients develop delayed motor and cognitive milestones, truncal and limb hypertonia, dyskinesia, tremor, dystonia, choreoathetosis, and seizures. Patients with DHPR deficiency are at increased risk of sudden death.

This disorder should be suspected in babies with hyperphenylalaninaemia identified through neonatal blood spot screening. DHPR enzyme activity measured in blood spots is markedly reduced. Concentrations of HVA, 5-HIAA, and folate are low and biopterin concentration is raised in CSF.[33] BH_4 deficiency is not always seen.[62] White-matter abnormalities and basal ganglia calcification might be evident on brain MRI.[33,58]

DHPR deficiency is caused by mutations in QDPR (OMIM *612676) on chromosome 4p15.31. Some mutations have been described.[50] Two mutations (Gly151Ser and Phe2112Cys) are associated with mild disease presentations, associated with selective impairment of serotonin metabolism.[63] DHPR deficiency results from a defect in the salvage pathway necessary for the regeneration of BH_4 after hydroxylation of substrates and the action of carbinolamine dehydratase (figure 2). A subsequent deficiency in regenerated BH_4, as well as the inhibitory effect of accumulated q-dihydrobiopterin on AADC, phenylalanine hydroxylase, tyrosine hydroxylase, and tryptophan hydroxlyase, results in hyperphenylalaninaemia and reduced production of dopamine and serotonin.[6] Neurological impairment might also be attributable to depleted folate concentrations in the brain, owing to the importance of DHPR in maintaining folate in its active form;[64] this feature is thought to raise the risk of sudden death. Accumulated q-dihydrobiopterin could also alter folic-acid concentrations.

Patients with DHPR deficiency require supplementation with BH_4, and some severely affected children also need dietary restriction of phenylalanine to normalise concentrations.[33] Neurotransmitter precursors (levodopa and 5-hydroxytryptophan) and other agents, such as monoamine oxidase inhibitors (eg, selegiline, tranylcypromine, and moclobemide), are frequently required. All doses should be started low and increased gradually to therapeutic levels to keep to a minimum the risk of dyskinesias and intolerance. Treatment with folinic acid is also recommended to counteract the depletion of folate caused by the disease and by levodopa therapy and, ultimately, to prevent secondary 5-methyl-tetrahydrofolate deficiency. Good clinical outcomes can be achieved,[33] especially if treatment is started early in the disease course.

Pterin-4a-carbinolamine dehydratase deficiency

Although transient neonatal hypotonia owing to pterin-4α-carbinolamine dehydratase deficiency (OMIM #264070) has been reported in some patients, most develop no neurological symptoms or signs and neurotransmitter abnormalities are not detected.[33] The clinical outcome is generally excellent.

Disorders of monoamine synthesis

Tyrosine hydroxylase deficiency

Tyrosine hydroxylase deficiency (OMIM #605407; also known as autosomal recessive Segawa syndrome, infantile parkisonism, dopa-responsive dystonia, and DYT5b) was reported in 1971 as a clinical syndrome characterised by early-onset, progressive, levodopa-responsive dystonia.[65] Around 50 patients worldwide have been reported so far.[66]

Tyrosine hydroxylase deficiency is classified as having two major subgroups: progressive hypokinetic rigid syndrome with dystonia (type A) and complex encephalopathy of neonatal or early-infancy onset (type B).[66] The two phenotypes do, however, overlap substantially.

Type A disease affects around 70% of patients. Of these, most present in infancy with a generalised parkinsonian phenotype characterised by hypokinesia, bradykinesia, and rigidity, and, rarely, clinical features of type B disease. Severity of dystonia varies and can be paroxysmal and have diurnal fluctuations in the early stages. Other patients with type A tyrosine hydroxylase deficiency present later in childhood (generally by age 5 years),[66] with gait instability and walking difficulties.[66] Over time, motor symptoms become generalised. Mild progressive mental retardation is frequently reported in patients who are younger than 1 year at presentation, but cognitive function seems less affected in children who present later.

Most children with type B tyrosine hydroxylase deficiency present within the first 3 months of life with severe parkinsonism and hypotonia. Mental retardation is also seen in most patients with type B disease, but is

thought to be nonprogressive. Focal or generalised dystonia with intermittent dystonic crises, oculogyric crises, myoclonus, tremor, dyskinesia, and ptosis have been reported. Autonomic features (sweating, temperature instability, hyperpyrexia, and drooling) and other neurological features, such as epileptic seizures and non-epileptic paroxysms, are also reported.[66]

Type A tyrosine hydroxylase deficiency can strongly mimic cerebral palsy or hereditary or acquired forms of juvenile parkinsonism,[66] whereas type B is frequently associated with perinatal complications and can be difficult to clinically distinguish from infectious, hypoxic ischaemic, epileptic, and metabolic (including mitochondrial) encephalopathies. Biochemical and genetic investigations should be done to confirm the diagnosis. In both types of tyrosine hydroxylase deficiency HVA concentration is decreased in CSF, but that of 5-HIAA remains normal.[30,66] A notably low ratio of HVA to 5-HIAA is seen in patients with early disease onset and in those with the type B phenotype. In around 50% of patients with tyrosine hydroxylase deficiency, hyperprolactinaemia, which manifests in a few patients as galactorrhoea, is reported.[35] MRI of the brain is normal in most patients but some children—most frequently those with type B disease—have non-specific white-matter abnormalities and increased extracerebral CSF spaces.[66]

Tyrosine hydroxylase deficiency is caused by mutations in *TH* (OMIM *191290) on chromosome 11p15.5. Roughly 100 mutations have been reported, of which most are missense variants that functionally lead to partial loss of enzyme activity.[66] Truncating mutations account for only 5% of reported mutations and so far in both disease subtypes have been heterozygous with a missense mutation on the other allele. A case of tyrosine hydroxylase deficiency associated with a large heterozygous deletion (encompassing several exons) was detected with multiplex ligation-dependent probe amplification.[67] The patient had a second pathogenic promoter mutation (1–70delG>A). No homozygous or compound heterozygous truncating mutations have been reported, but findings from a knockout mouse model suggest that the complete loss of tyrosine hydroxylase would be fatal.[68] Although most mutations are restricted to within a family, some common mutations are reported (70G→A, 707T→C in patients of Greek origin, and a Dutch founder effect for 698G→A).[66,69] Patients with at least one promoter mutation seem to have type A disease or a mild phenotype,[66,67] which is thought to be related to notable residual tyrosine hydroxylase activity despite reduced *TH* transcription.

Tyrosine hydroxylase catalyses the conversion of tyrosine to levodihydroxyphenylalanine (L-dopa), which is the rate-limiting step in catecholamine biosynthesis (figure 2). Clinical symptoms, therefore, arise from cerebral catecholamine deficiency.[70]

Early diagnosis and prompt therapeutic intervention are thought to improve motor and cognitive outcome in patients with tyrosine hydroxylase deficiency: a baby with a diagnosis made by analysis of CSF at age 8 months and treated immediately with slow-release combined levodopa and carbidopa[71] had normal cognitive and motor functions at age 17 years (Clayton PT, unpublished). Combined levodopa and carbidopa is the preferred first-line regimen.[66] In most patients with type A disease, initial levodopa doses of 3 mg/kg daily are generally tolerated if given in three divided doses. Some patients with type B disease, however, might be hypersensitive to levodopa, and a very low starting dose (<0·5 mg/kg daily) with treatment given as four to six divided doses per day and very gradual increases are recommended. Patients should be monitored carefully for dyskinesias and other adverse effects. Other drugs (dopamine agonists, anticholinergics, monoamine oxidase inhibitors, and benzodiazepines) are used only rarely. Response to levodopa is much more apparent in patients with type A tyrosine hydroxylase deficiency than in those with type B disease and is especially good in type A patients with promoter mutations. A high ratio of HVA to 5-HIAA is indicative of increased residual TH activity, which is associated with a good response to levodopa. Impaired cognitive function persists even in patients who respond to treatment, although further cognitive regression is unlikely. Intrauterine dopamine deficiency might cause aberrant prenatal brain development, which could contribute to postnatal mental retardation.

AADC deficiency
Since this disorder was first reported in 1990,[72] fewer than 100 patients with AADC deficiency (OMIM #608643) have been reported worldwide.[73]

Reported ages of clinical presentation have been from around age 4 months to 24 years, but most patients present during infancy and childhood.[73] Hypotonia and oculogyric crises are the two main characteristics at presentation. Around 50% of patients have a movement disorder, such as hypokinesia, choreoathetosis, dystonia, or bulbar dysfunction (feeding and speech difficulties). Eye abnormalities, such as ptosis and poor visual fixation, are also reported. Sleeping difficulties, autonomic dysfunction, temperature instability, irritability, and nasal congestion might be seen. Cognitive impairment affects most patients.

AADC deficiency can mimic many neuromuscular disorders, such as myasthenia, and metabolic diseases, such as mitochondrial encephalopathies, as well as hypotonic cerebral palsy, other early-onset disorders of dopamine metabolism, and hyperekplexia.

Characteristic findings in CSF include notably low concentrations of HVA, 5-HIAA, and 3-methoxy-4-hydroxyphenylglycol, with raised concentrations of 5-hydroxytryptophan, L-dopa, and 3-ortho-methyldopa.[30,73] AADC activity in plasma is very low to undetectable. High urinary concentrations of vanillactic acid and 3-ortho-methyldopa are seen in some patients, and the latter is being investigated as a useful rapid screening tool for

AADC deficiency (Lumsden DE, Evelina Children's Hospital, London, UK, personal communication). In general, no brain abnormalities are seen on MRI, but non-specific changes, such as cerebral atrophy, degenerative white-matter changes, abnormal myelination, and thinning of the corpus callosum, have been reported.[73] Electroencephalographic abnormalities, such as slow or fast activity and polyspikes, have also described.[73]

AADC deficiency is caused by mutations in *DDC* (OMIM *107930) on chromosome 7p12.3–p12.1, but there are no reported mutation hotspots or genotype–phenotype correlations. Most mutations are within families, although the splice-site mutation IVS6+4A→T seems to be a founder mutation in individuals of Chinese origin.[73] Mutations in *DDC* lead to reductions in AADC activity and clinical features reflect the severe resultant combined catecholamine and serotonin deficiency (figure 2).

The aim of treatment in AADC deficiency is to correct the neurotransmitter abnormalities.[73] Few patients, however, respond well[73] and clinical improvement is reported in only around 20%. Augmentation of residual AADC activity is achieved by supplementation with its cofactor pyridoxal phosphate to a maximum dose of 200 mg/kg daily. 10–20 mg folinic acid daily is given to counteract folate depletion in CSF, which is caused by methylation of accumulated L-dopa. Dopamine agonists (bromocriptine or pergolide) and monoamine oxidase inhibitors (selegiline or tranylcypromine) are frequently used. Fibrosis (eg, of the heart valves) is a risk with pergolide therapy, but no such complication has been reported in patients with AADC deficiency. Regular monitoring with echocardiography is, however, recommended. Dystonia can be treated with the anticholinergic drug trihexyphenidyl. Levodopa is used rarely and generally without carbidopa. If it is used, starting doses must be very low and given as four to six divided doses per day, with very gradual increase to therapeutic doses to prevent complications of receptor hypersensitivity in severe cases. Response to levodopa is poor in most patients and a strong response has been reported only in patients who have mutations that affect AADC binding to levodopa.[74]

Inherited abnormalities of vitamin B6 metabolism

Pyridoxal phosphate is an essential cofactor for the reactions catalysed by AADC.[75,76] Autosomal recessive pyridoxamine 5′-phosphate oxidase deficiency (OMIM #610090) leads to reductions in synthesis of pyridoxal phosphate from pyridoxine and pyridoxamine and probably reductions in recycling of pyridoxal phosphate from pyridoxamine phosphate, which impairs dopamine and serotonin production.

Some children present with severe, potentially fatal, anticonvulsant-resistant neonatal encephalopathy, frequently with a history of prenatal seizure onset.[30,77] Many affected children have seizures of various types that can be of long duration. The risk of premature birth

is high. This deficiency can mimic other infantile epileptic encephalopathies of metabolic, acquired (hypoxic ischaemic encephalopathy), structural, or genetic origin, and the biochemical features might be similar to those seen in some cases of pyridoxine-dependent epilepsy due to mutations in the antiquitin gene.[78] The biochemical and, to a lesser extent, clinical features can mimic AADC deficiency.

Electroencephalography might show a burst suppression pattern. Neonatal hypoglycaemia and lactic acidosis have been reported.[79] Analysis of neuro-transmitters in CSF shows a similar profile to that seen in AADC deficiency and some cases of pyridoxine-dependent epilepsy (low HVA and 5-HIAA concentrations and high L-dopa, 5-hydroxytryptophan, and 3-ortho-methyldopa concentrations).[30,73,78] AADC should be excluded by measurement of AADC activity, and pyridoxine-dependent epilepsy (due to antiquitin mutations) by measurement of urinary α-aminoadipic semialdehyde. Additional CSF abnormalities in pyridoxamine 5′-phosphate oxidase deficiency include raised glycine, taurine, histidine, and threonine, and low arginine levels. Urinary vanillactic acid levels might also be raised.

Pyridoxamine 5′-phosphate oxidase deficiency is caused by mutations in *PNPO* (*603287) on chromosome 17q21.32.[76] A wide variety of mutations have been described.

Patients with PNPO deficiency respond to treatment with pyridoxal phosphate but not pyridoxine. For suspected cases, pyridoxal phosphate should be trialled at 30 mg/kg daily given as three to four divided enteral doses per day for 3–5 days. In confirmed cases 30–50 mg/kg pyridoxal phosphate daily in four to six divided doses may be used long term.[79] If a vitamin B6 defect is suspected, a trial of pyridoxine followed by a trial of pyridoxal phosphate might help to distinguish between pyridoxine-dependent and pyridoxal-phosphate-dependent disorders.

Disorders of monoamine transport

Although most primary monoamine-deficiency disorders result from defective biosynthesis, defects in monoamine transport also cause such disorders.

All children with autosomal recessive DTDS (OMIM #613135) present in early infancy with a complex motor disorder characterised by hyperkinesia (orolingual and limb dyskinesia, dystonia, and chorea), hypokinesia, or a hyperkinetic and hypokinetic mixed phenotype.[80,81] Most children develop progressive generalised dystonia, and some have dystonic storms or episodic status dystonicus. Parkinsonism (bradykinesia, hypomimia, rigidity, and resting tremor) and axial hypotonia are also early disease features. Pyramidal tract features are seen during childhood. An eye movement disorder that features ocular flutter, saccade initiation failure, eyelid myoclonus, and oculogyric crises might also be seen. In the DTDS cases

described, cognitive function seems to be less severely affected than motor function. Other features include sleeping difficulties, orthopaedic complications, and cardiorespiratory insufficiency (secondary to frequent pneumonias and cardiac failure). The mean life expectancy is 13·6 years.[81]

Many patients with DTDS are misdiagnosed as having dyskinetic cerebral palsy. Other clinically similar syndromes include mitochondrial cytopathies, infantile-onset dopamine or pterin biosynthetic defects, and other infantile-onset movement disorders (eg, neurodegeneration with brain iron accumulation).[81] The neurotransmitter profile in CSF is characterised by a raised ratio of HVA to 5-HIAA.[80–82] High concentrations of prolactin and creatine kinase in serum are seen in some patients.[81] SPECT with ioflupane (123I) in one patient showed complete loss of dopamine transporter activity in the basal nuclei.[81]

Patients have homozygous or compound heterozygous loss-of-function mutations in *SLC6A3* (OMIM *126455), the gene encoding the dopamine transporter, on chromosome 5p15.3.[81,82] Most detected mutations (61%) are missense mutations.[81] No common mutations or mutation hotspots are yet known within the coding region of the gene. Defective presynaptic reuptake of dopamine is thought to lead to accumulation of synaptic dopamine, which is catabolised and results in raised HVA concentrations in CSF.[83] Dopamine-transporter defects do not affect the serotonin biosynthetic pathway and, therefore, concentrations of 5-HIAA in CSF are normal. Poor dopamine reuptake leads to depleted presynaptic stores of intracellular dopamine for extraneuronal release. Excess extraneuronal dopamine might also overstimulate presynaptic D2 autoreceptors, which results in inhibition of tyrosine hydroxylase and decreased de novo dopamine production.[83] Excess extraneuronal dopamine might have postsynaptic effects, such as downregulation or desensitisation of postsynaptic dopamine receptors, with alterations in downstream signalling.[81,83]

Treatment has little effect on DTDS.[81] Dopamine agonists (pramipexole and ropinirole) have led to some clinical improvements in motor symptoms in a few patients, but the optimum doses, adverse-effect profiles in children, and long-term benefits remain unclear. Insertion of a deep-brain stimulator in the early stages of disease might be a feasible therapeutic option in the future.

Disorders of selective serotonin deficiency
A distinct group of patients present with motor disorders associated with an isolated decrease in 5-HIAA production. Naumann and colleagues[84] have reported a series of adult patients with idiopathic adult-onset dystonia in which 5-HIAA levels were significantly lower than those in controls. 5-HIAA concentrations might also be reduced in other adult neurological disorders, such as cerebellar tremor, neuropsychiatric disorders, and Alzheimer's disease. The observation that patients with dystonia are more susceptible to depression could be consistent with a pathological reduction in serotonin activity. Assmann and colleagues[85] have reported a series of paediatric patients with a selective decrease in serotonin turnover associated with dystonia unresponsive to levodopa treatment. In these patients, 5-HIAA concentrations in CSF were 50% lower than those in a reference population of children with levodopa-responsive dystonia. Some children had a dystonic disorder of undetermined cause, and in others (with hypoxic ischaemic encephalopathy, Pelizaeus-Merzbacher disease, pantothenate kinase-associated neurodegeneration, pontocerebellar hypoplasia, cerebral palsy, and paroxysmal kinesogenic dyskinesia) dystonic symptoms were thought to be secondary to the primary diagnosis.

The mechanism of disease is unclear and no causative genes have yet been identified. The variety of clinical presentations could indicate heterogeneity in underlying causes. Some cases might be associated with inherited defects in serotonin biosynthesis, release, transport, or degradation. De Grandis and colleagues[86] undertook mutational analysis of *TPH2* in five patients who presented with psychomotor delay (two), epileptic encephalopathy (one), a movement disorder (one), or an autistic spectrum disorder (one), and low 5-HIAA concentrations with no clear cause. No pathogenic *TPH2* mutations were detected. Another possible pathophysiological mechanism is serotoninergic tract degeneration.[84,85]

Treatment with drugs that increase serotonin concentration in the synaptic cleft (eg, selective serotonin-reuptake inhibitors and 5-hydroxytryptophan) could be considered.

Secondary neurotransmitter disorders
Neurotransmitters abnormalities indicative of dopamine or serotonin depletion are becoming increasingly recognised as secondary phenomena in several neurological disorders. Concentrations of HVA and 5-HIAA in CSF in such patients are mostly within the range deemed abnormal for primary neurotransmitter disorders, but generally do not reach the lowest levels.

A secondary reduction in HVA is reported in perinatal asphyxia, disorders of folate metabolism, phenylketonuria, Lesch-Nyhan disease, mitochondrial disorders, epilepsy (and infantile spasms), opsoclonus-myoclonus, pontocerebellar hypoplasia, leukodystrophies, Rett's syndrome, and some neuropsychiatric disorders.[30,87–89] Many patients who have no specific diagnosis but who present with neuromuscular or dystonic symptoms have low HVA concentrations in CSF, which suggests dopaminergic depletion. These patients also often present with dyskinesia, tremor, and eye-movement disorders similar to those seen in many of the primary monoamine neurotransmitter disorders. Cortical atrophy is associated

with low levels of 5-HIAA in CSF. Low concentrations of HVA and 5-HIAA have been reported in patients with type 2 pontocerebellar hypoplasia[30,88] and in a syndrome that involves spontaneous periodic hypothermia and hyperhidrosis.[90] Whether the latter syndrome is a primary or secondary neurotransmitter disorder is still unclear because the underlying cause is unknown.

Patients with neonatal disease onset who have severe motor deficits and abnormalities on brain MRI seem particularly vulnerable to secondary reductions in HVA production.[88] Such disruption of normal brain function is likely to impair biogenic monoamine synthesis, and the resultant neurotransmitter deficiencies in critical periods of neurodevelopment are thought to prevent development of certain brain functions. The possibility of treating such patients with levodopa, 5-hydroxytryptophan, or both should be considered, therefore, to improve brain maturation and neurological outcome.

Conclusions

The monoamine neurotransmitter disorders are an expanding group of neurological syndromes, many of which present in infancy and early childhood (table). They are important to recognise because they are frequently misdiagnosed and many show a good clinical response to treatment. Increased clinical awareness, reliable and reproducible biochemical testing, and advances in molecular genetic testing have improved delineation of the phenotypic spectrum of such disorders. Analysis of neurotransmitters in CSF is increasingly being done in patients with motor deficits, which has led to the identification of new disorders in which the underlying neurotransmitter defect is either unresolved or the monoamine abnormalities are secondary phenomena.

Detailed clinical history and physical examination, appropriate assessments of neurotransmitters in CSF, targeted genetic screening, and definitive exclusion of disorders mimicking neurotransmitter disorders will help with accurate diagnosis and appropriate treatment.

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