Expert to Expert:
Paediatric Movement Disorders

Pre-course Reading

Bristol
18-19 October 2018
DEFINITIONS
Dystonia is a movement disorder in which involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both. Dystonia in cerebral palsy (CP) presents as hypertonia, involuntary postures and movements, or a combination. Dystonia occurs in dyskinetic CP but also is commonly present in spastic CP.

WHY IS DYSTONIA IN CEREBRAL PALSY IMPORTANT?
- Dystonia can impede motor function through involuntary muscle contractions, limitations in muscle relaxation, and overflow, which is the association of involuntary movement with intended movement which spreads to surrounding or distant muscles.
- Dystonia can interfere with positioning for sitting and lying.
- Dystonic postures and movement can be painful.
- Dystonia can interfere with sleep.
- Dystonia can result in high energy expenditure and malnutrition.
- Dystonic postures/hypertonia can create challenges with care-giving.

Target Population: Individuals with dystonia in CP where the dystonia interferes with function, positioning or causes pain and disrupted sleep.

Target Clinical Providers: Physicians/Nurses/Therapists caring for individuals with dystonia in CP.

ASSESSMENT
Dystonia is a frequently overlooked element of the neurological presentation of CP. Therefore, it is recommended that a `dystonia` assessment be routinely included in your neurological examination (assessing for fluctuating hypertonia, and using tactile stimulation or voluntary movement to trigger dystonia). More information can be found in Section 3 of this pathway in the HAT tool link. On your examination, determine if the dystonia is generalized or focal and assess the severity (can use a standardized scale such as the Barry Albright Dystonia Scale outlined in Section 3). Assess the impact of the dystonia on function, pain/comfort (including sleep), and care-giving and whether management is required.

If dystonia is present, assess whether the neurologic presentation is consistent with CP (risk factors, brain imaging, and family history) or if additional work-up is required. An important masquerader of CP-related dystonia is Dopamine Responsive Dystonia. Consider the need for a trial of levodopa and/or a referral to a neurologist/geneticist for additional diagnostic work-up.

MANAGEMENT
It is important to note that much of this Dystonia Care Pathway is based on expert opinion, as the evidence for dystonia management in CP is currently limited.

- Rehabilitation Strategies: Rehabilitation strategies used by physiotherapists, occupational therapists and speech pathologists are generally considered cornerstones in the management of dystonia in CP. General principles include: 1) ensuring therapy is goal-directed, 2) avoiding asymmetry and aiming for symmetrical positioning to enhance motor control, 3) optimizing seating and positioning with good stability/support, 4) considering orthoses and splints to increase stability and coordination, and 5) considering the need for communication supports.

- Generalized Dystonia Management: With increasing severity of dystonia, additional interventions may be required beginning with oral medications. Oral baclofen is considered a first line medication for the management of dystonia in CP. Common indications include pain or difficulty sleeping associated with dystonia in CP. If the individual does not respond well to oral baclofen, trihexyphenidyl can be used as a second line medication. Other oral medications should be considered for specific indications. For example, the intermittent use of benzodiazepines is helpful for dystonic storms or disturbed sleep, and gabapentin for dystonia associated with pain.
Clonidine can also be considered for disturbed sleep associated with dystonia.

In the presence of severe generalized dystonia associated with significant impact on care/comfort, more aggressive management can be undertaken. This may include intrathecal baclofen (ITB) or deep brain stimulation (DBS). These strategies require a referral to a specialist team. Individuals with severe generalized hypertonia with a combination of dystonia and spasticity may trial intrathecal baclofen. Other considerations of whether to choose ITB or DBS can be based on the cerebral anatomy and whether placement of the stimulator in the globus pallidus is possible. ITB should be used with caution in the presence of nocturnal respiratory compromise.

A classic feature of dystonia in CP is a fluctuation in the severity of the dystonia. For this reason it is important to periodically re-evaluate the individual and adjust the interventions as required. For some individuals with severe dystonia, a personalized plan for managing increasing dystonia can be developed and includes increasing the dose of current oral medications or introducing a second medication (e.g. clonidine or gabapentin). The use of the Dystonia Severity Action Plan (DSAP) may be helpful for monitoring unstable dystonia and is outlined in Section 3. A rapid and severe increase in dystonia is termed ‘Periodic Status Dystonicus’. It can be life-threatening and requires urgent treatment often with a combination of benzodiazepines and clonidine (enteral, intravenous, or transdermal) (see Section 3 for a management protocol for ‘Status Dystonicus’). Another important issue is the triggering of dystonia from secondary health conditions including gastrointestinal disorders such as reflux or constipation. The overall general health of the individual should be carefully monitored and secondary health issues actively addressed.

- **Focal Dystonia Management**: For individuals with focal or segmental dystonia associated with persisting postures causing pain or impacting on function/care-giving, periodic injections of Botulinum toxin can be undertaken. Consider targeting both the agonist/antagonist muscles around the joint(s) involved with the dystonic posture.
The purpose of this document is to provide health care professionals with key facts and recommendations for the assessment and treatment of dystonia in children and youth with cerebral palsy. This summary was produced by the AACPDM Dystonia Care Pathway Team (D Fehlings (team lead), L Brown, A Harvey, K Himmelmann, JP Lin, A Macintosh, J Mink, E Monballu, J Rice, J Silver, L Switzer, I Walters). The summary is based on a systematic review being submitted for peer-reviewed publication. However, health care professionals should continue to use their own judgement and take into account additional relevant factors and context. The AACPDM is not liable for any damages, claims, liabilities, or costs arising from the use of these recommendations including loss or damages arising from any claims made by a third party.
**Monoamine neurotransmitter disorders—clinical advances and future perspectives**

Joanne Ng, Apostolos Papandreou, Simon J. Heales and Manju A. Kurian

**Abstract** | The monoamine neurotransmitter disorders are important genetic syndromes that cause disturbances in catecholamine (dopamine, noradrenaline and adrenaline) and serotonin homeostasis. These disorders result in aberrant monoamine synthesis, metabolism and transport. The clinical phenotypes are predominantly neurological, and symptoms resemble other childhood neurological disorders, such as dystonic or dyskinetic cerebral palsy, hypoxic ischaemic encephalopathy and movement disorders. As a consequence, monoamine neurotransmitter disorders are under-recognized and often misdiagnosed. The diagnosis of monoamine neurotransmitter disorders requires detailed clinical assessment, cerebrospinal fluid neurotransmitter analysis and further supportive diagnostic investigations. Prompt and accurate diagnosis of neurotransmitter disorders is paramount, as many are responsive to treatment. The treatment is usually mechanism-based, with the aim to reverse disturbances of monoamine synthesis and/or metabolism. Therapeutic intervention can lead to complete resolution of motor symptoms in some conditions, and considerably improve quality of life in others. In this Review, we discuss the clinical features, diagnosis and management of monoamine neurotransmitter disorders, and consider novel concepts, the latest advances in research and future prospects for therapy.

Ng, J. et al. Nat. Rev. Neurol. 11, 567–584 (2015); published online 22 September 2015; doi:10.1038/nrneurol.2015.172

**Introduction**

Monoamine neurotransmitters are essential for signalling in the CNS and PNS, and are involved in the regulation of movement, basal muscle tone, activity levels, mood, attention, sleep, vascular tone, circulation, thermoregulation and pain modulation. Inherited disorders of monoamine synthesis, metabolism and transport are a growing group of genetic conditions that result in impaired biogenic amine homeostasis.

Several primary and secondary monoamine neurotransmitter disorders are known (Figure 1), and knowledge of monoamine metabolism and homeostasis is invaluable for accurate diagnosis and effective treatment of these disorders. Monoamines are synthesized in presynaptic neurons and packaged into vesicles by synaptic vesicular amine transporter (also known as vesicular monoamine transporter 2; VMAT2) for subsequent release into the synaptic cleft, where they bind to postsynaptic receptors. Neurotransmission is terminated by degradation or reuptake of the monoamine (Figure 2).

In this Review, we describe the key clinical features that indicate a monoamine neurotransmitter disorder, and discuss diagnostic investigations, current treatment strategies, advances in therapeutics, and future perspectives.

**Diagnosis of neurotransmitter disorders**

Neurotransmitter disorders can be diagnosed by combining information from a patient’s clinical history with the findings of physical examination, specific biochemical investigations and genetic testing (Figure 3). The key steps in diagnosing these conditions are described below. Further support in the clinical assessment and investigation of these diseases is available from other resources.

**History and examination**

Disruption of monoamine metabolism leads to diverse neurological manifestations in childhood that are evident from a clinical history and examination. For some patients, the family history reveals consanguinity, which might indicate a recessive inherited disorder. The presentation of the disorders can include cognitive and motor delay, epilepsy, autonomic dysfunction (which manifests as sweating, temperature dysregulation, hypersalivation and nasal congestion) and neuropsychiatric features such as anxiety or autistic spectrum disorder. Motor symptoms are often prominent and include gait disturbances, dystonia, dyskinesia, parkinsonism, tremor, oculogetic crises, palpebral ptosis and axial hypotonia. Patients often exhibit diurnal variation: motor symptoms become more prominent in the evening and improve after sleep. Other associated features include feeding difficulties and microcephaly.

Many clinical features of monoamine neurotransmitter disorders are observed in other neurological conditions, such as cerebral palsy, primary movement disorders, paroxysmal disorders, hypoxic–ischaemic encephalopathy and epileptic encephalopathies. These shared features result in frequent misdiagnosis and under-recognition of monoamine neurotransmitter disorders.

**Competing interests**

The authors declare no competing interests.
Key points

- Monoamine neurotransmitter disorders are under-recognized and often misdiagnosed, as many mimic cerebral palsy and other neurological disorders
- ‘Red flag’ symptoms of monoamine neurotransmitter disorders include diurnal variation of symptoms, a mixed movement disorder, autonomic disturbance, involvement of the eyes (ptosis, oculogyric crisis) and levodopa responsiveness
- Many monoamine neurotransmitter disorders are amenable to treatment; appropriate therapy is curative in some disorders
- Analysis of cerebrospinal fluid neurotransmitter levels aids identification of the specific monoamine pathway defect and is vital for accurate diagnosis of most primary neurotransmitter disorders and selection of appropriate disease-specific pharmacotherapy
- Research in the past few years has identified novel monoamine neurotransmitter disorders that involve defects in dopamine transport and monoamine vesicle packaging
- Discoveries of novel genetic defects and biomarkers in monoamine neurotransmitter disorders, together with novel disease models, will improve our understanding of pathophysiological mechanisms and facilitate the development of new treatments

Cerebrospinal fluid analysis

An abnormal cerebrospinal fluid (CSF) neurotransmitter profile is one of the most important indicators of a neurotransmitter disorder (Figure 3).\(^{7,9,10}\) CSF is analysed at specialist centres with high-performance liquid chromatography\(^{1,6,11,12}\) to measure levels of homovanillic acid (HVA), 3-O-methyl-dopa (3-OMD), 3-methoxy-4-hydroxyphenylglycol (MHPG), 5-hydroxyindoleacetic acid (5-HIAA), neopterin, tetrahydrobiopterin (BH4), dihydrobiopterin (BH2) 5-methyltetrahydrofolate and pyridoxal 5′-phosphate (vitamin B6). CSF levels of glucose, lactate and amino acids are often analysed at the same time, especially in children with undiagnosed neurological symptoms.

Analysis of CSF requires the use of strict protocols to ensure accurate results (Box 1).\(^{5,12}\) Care must also be taken to ensure the correct interpretation of results. The time of day at which the CSF sample is taken should be recorded because HVA concentrations might decline in the evening in some dopa-responsive pterin synthesis defects. Medication that the patient is receiving at the time of CSF sampling should also be documented, as some drugs (for example levodopa) can affect CSF neurotransmitter levels. Furthermore, results should be compared with those from age-matched references because CSF concentrations of HVA, 5-HIAA and BH4 are high at birth, rapidly decrease in the first few months of life, then decrease slowly into adulthood.\(^{13}\)

Neurotransmitter disorders can be missed with CSF analysis. A common misperception is that neurotransmitter levels must markedly differ from age-matched normal levels to indicate a neurotransmitter disorder; in fact differences might be subtle. In GTP cyclohydrolase 1 (GTP-CH 1) deficiency, the CSF neurotransmitter profile can be normal,\(^{14}\) so the clinical presentation and response to levodopa are key to the diagnosis of this condition. Furthermore, several therapies can alter CSF neurotransmitter profiles. Children with movement disorders often receive a trial of medication that masks neurotransmitter abnormalities. In deficiencies of GTP-CH 1,\(^{14}\) 6-pyruvoyl tetrahydropterin synthase (PTPS)\(^{15}\) and tyrosine hydroxylase, treatment with levodopa can normalize HVA levels, but concomitant abnormal levels of 3-OMD indicate the use of levodopa therapy in this situation.\(^{16}\) Treatment with 5-hydroxytryptophan can normalize levels of 5-HIAA, and tetrahydrobiopterin therapy can normalize BH4.

Blood and urine analysis

Analysis of blood and urine to detect metabolites of pterins and biogenic amines can facilitate diagnosis of a monoamine neurotransmitter disorder (Figure 4).

Hyperphenylalaninaemia associated with pterin defects can be detected with the neonatal dried blood spot (DBS) screening test and plasma amino acid analysis (Figure 4). High plasma levels of prolactin, especially in the context of galactorrhoea,\(^{17}\) can be a manifestation of central dopaminergic deficiency, as dopamine has a physiological role in suppressing prolactin release,\(^{18}\) although normal levels do not exclude a neurotransmitter disorder.\(^{19}\) Prolactin levels should be interpreted using age-related reference ranges.\(^{19}\)

Urine levels of neopterin and biopterin can indicate pterin defects, and high urine levels of vanillylactic acid can indicate aromatic L-amin acid decarboxylase (AADC) deficiency or, in some patients, pyridoxine 5′-phosphate oxidase (PNPO) deficiency.\(^{19}\) In dopamine transporter deficiency syndrome (DTDS), the HVA:creatinine ratio in urine is sometimes high,\(^{20,21}\) and urinary HVA and 5-HIAA levels are high in brain dopamine–serotonin vesicular transport disease (Figure 4).\(^{22}\)

Enzyme assays

Measuring enzyme activity can be helpful for diagnosis of a monoamine neurotransmitter disorder, particularly when such a disorder is suspected but CSF neurotransmitter analysis is atypical for the suspected condition and genetic testing identifies no disease-causing mutation. For example, activity of fibroblast GTP-CH 1 can be measured when GTP-CH 1 deficiency is suspected but the patient does not exhibit the classic response to levodopa, their CSF neurotransmitter profile is normal or atypical for the condition, and/or no mutation is detected in the GCH1 gene.\(^{7}\) Enzyme assays can also help in the diagnosis of sepiapterin reductase deficiency, dihydropteridine reductase deficiency and AADC deficiency (Figure 4).\(^{7}\)

Phenylalanine loading test

The phenylalanine loading test is an adjunctive diagnostic test for pterin disorders with no hyperphenylalaninaemia.\(^{23,24}\) An increased phenylalanine–tyrosine ratio in the serum after oral administration of a phenylalanine load (100 mg/kg) indicates a BH4 metabolism defect. Serial ratio measurements after loading demonstrates an initially increased ratio that subsequently declines,\(^{28}\) although in practice, a single measurement at 2 h after loading might suffice if levels of bipterin are reduced.\(^{7}\) Normal tyrosine levels in follow-up phenylalanine loading after BH4 supplementation provides
Further evidence for a pterin defect. The phenylalanine loading test should not be conducted in patients who are receiving treatment with BH4, as the phenylalanine concentration profile remains normal in this situation.20

The phenylalanine loading test is neither 100% sensitive nor 100% specific for pterin defects. False negative results can be seen in patients with GTP-CH I deficiency, and false positive results in heterozygote carriers of phenylalanine hydroxylase mutations.23

**Trial of levodopa**

Treatment with levodopa aims to restore dopamine levels in disorders of dopamine synthesis, and responsiveness to this treatment can be vital for the diagnosis of monoamine neurotransmitter disorders. Patients with GTP-CH I deficiency exhibit an excellent response to levodopa, so a levodopa trial is a major diagnostic tool in this disorder.26 Deficiencies of tyrosine hydroxylase,16 sepiapterin reductase27 and PTPS also respond to levodopa to some degree.13 Dopa-responsive dystonia with onset in the first decade of life could also indicate juvenile parkinsonism associated, for example, with PARK2 mutations.28

Levodopa should be administered with a peripheral inhibitor of AADC, such as carbidopa or benserazide, to prevent conversion of the drug to dopamine in the periphery. Treatment should be commenced at a low dose that is gradually titrated according to the patient’s tolerance and response, so as to minimize the risk of levodopa-induced dyskinesia. The development of variable-intensity dyskinesia with responsiveness to levodopa can indicate specific neurotransmitter disorders, such as tyrosine hydroxylase deficiency.29 If dyskinesia develops, it can often be eliminated by reducing the dose of levodopa. Gastrointestinal symptoms are commonly experienced by children on levodopa and are often managed with prophylactic antiemetics.7

**Molecular genetics**

Mutational analysis of specific genes can confirm the diagnosis of monoamine neurotransmitter disorders. Genetic confirmation enables appropriate genetic counselling for affected families, appropriate testing of extended family, prenatal testing, and preimplantation diagnosis. Genetic confirmation of a diagnosis can also help to assess the prognosis, as correlations have been reported between genotype and phenotype in several disorders, including tyrosine hydroxylase deficiency, PTPS deficiency and DTDS.16,31,32 Some monoamine neurotransmitter disorders can be detected with microarray studies (for example, by determining copy number variants in dopamine β-hydroxylase deficiency)33 and, increasingly, with whole exome and whole genome sequencing.
Primary disorders
Impaired tetrahydrobiopterin synthesis
BH4 is an essential cofactor in the hydroxylation of phenylalanine and is essential for monoamine synthesis. BH4 deficiencies encompass a heterogeneous group of defects in pterin synthesis or regeneration that occur with or without hyperphenylalaninaemia (Figure 2). These conditions are treatable, and thorough diagnostic investigations for BH4 deficiencies should be conducted in all patients with clinical symptoms of dopamine or serotonin deficiency, elevated phenylalanine levels detected by newborn DBS screening, or unexplained neurological symptoms.

Autosomal dominant GTP-CH 1 deficiency
GTP-CH 1 catalyses the conversion of GTP to dihydrobiopterin triphosphate, the rate-limiting step in BH4 synthesis. The incidence of autosomal dominant GTP-CH 1 deficiency (also known as Segawa disease, dopa-responsive dystonia or DYT5a) is 0.5 per 100,000
people, with a female: male ratio of 2.5:1. Patients typically present with postural dystonia that affects the lower limbs, with turning of the foot (pes equinovarus). Marked diurnal variation (classically referred to as evening dystonia), and a remarkable response to levodopa treatment (which resolves motor symptoms in most patients) are key, often diagnostic, features of the condition.

Segawa proposed an age-related clinical course of GTP-CH 1 deficiency, in which disease presentation and evolution relates to the development and maturation of the nigrostriatal pathways. Patients who develop the condition in middle childhood experience action dystonia, retrocollis and, in some patients, oculogyric crisis. Adolescents present with asymmetrical upper limb postural tremor, and adults present with upper limb tremor, parkinsonism and gait rigidity. Atypical movement phenotypes include writer's cramp and spasmodic dysphonia. Other conditions, such as diplegic cerebral
Box 1 | Collection and analysis of CSF samples

CSF samples must be snap frozen with liquid nitrogen or dry ice immediately after collection, as BH4 is labile, and subsequently stored at −80°C until it is analysed. Addition of the metal chelator diethylene triamine pentaacetic acid and the reducing agent dithioerythritol is required to prevent oxidation of BH4. Delayed or slow freezing can result in metabolite degradation that leads to erroneous results. Contamination with red blood cells also leads to rapid metabolite oxidation, so CSF samples should be immediately centrifuged and the clear supernatant transferred to new tubes for snap freezing. Three sequential samples of CSF are usually collected via a lumbar tap. The first is used to measure levels of HVA and 5-HIAA, the second to measure levels of 5-MTHF and pyridoxal 5′-phosphate, and the third to measure levels of pterins. All members of each metabolite group must be measured in the same sample because a rostrocaudal concentration gradient of CSF monoamine metabolites exists. For the same reason, the sampling method must be clearly identified, as metabolite concentrations might seem high if a ventricular CSF sample is compared with a reference sample obtained by lumbar puncture.

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; 5-MTHF, 5-methyltetrahydrofolate; BH4, tetrahydrobiopterin; CSF, cerebrospinal fluid; HVA, homovanillic acid.

palys, hereditary spastic paraparesis and paroxysmal exercise-induced dyskinesia, mimic GTP-CH 1 deficiency.8–10 Early-onset Parkinson disease has also been recognized in patients with GTP-CH 1 deficiency.41,42

Diagnosis of GTP-CH 1 deficiency is made using the results of biochemical tests, genetic analysis and a levodopa trial (Figures 3 and 4). Plasma phenylalanine levels are normal, and the phenylalanine loading test is often abnormal. Typically, the CSF neurotransmitter profile in GTP-CH 1 deficiency reveals low levels of HVA, 5-HIAA, BH4 and neopterin. However, levels of HVA and 5-HIAA might only be slightly reduced or normal, so the diagnosis can be missed on CSF analysis. Normal or subtly abnormal CSF neurotransmitter levels do not, therefore, exclude GTP-CH 1 deficiency, so genetic studies should still be conducted if the clinical features and levodopa response are consistent with the condition.40

To date, >100 different GCH1 mutations have been identified, which account for GTP-CH 1 deficiency in ~60% of patients. Direct sequencing identifies no mutations in the remaining ~40% of patients; in some of these individuals, large deletions and intragenic duplications, which can be identified by using multiplex ligation-dependent probe amplification, might be causative.44

In nearly all patients with classic GTP-CH 1 deficiency, levodopa treatment elicits a striking response (Table 1). If no response to levodopa treatment is seen, autosomal dominant GTP-CH 1 deficiency is unlikely. Typically, patients remain stable on levodopa treatment into adulthood, and the dose of levodopa often does not need to be increased with age or longer treatment. Indeed, for many patients, levodopa dosage can be decreased over time.43 In the long term, ~20% of adults on this treatment develop levodopa-related dyskinesia. In rare cases, a combination treatment of BH4 and levodopa has been used in an attempt to achieve complete resolution of symptoms. BH4 monotherapy was ineffective in animal models of GTP-CH 1 deficiency,46 and is reported to be clinically ineffective.44

Autosomal recessive GTP-CH 1 deficiency

The recessive form of GTP-CH 1 deficiency presents with truncal hypotonia, a wide variety of movement disorders (including dystonia), autonomic dysfunction, seizures and developmental delay. Hyperphenylalaninaemia, detected with newborn DBS screening, or high plasma levels of amino acids can help to distinguish the autosomal recessive form of the condition from the autosomal dominant form. However, several reports of autosomal recessive GTP-CH 1 deficiency that presents without hyperphenylalaninaemia suggest a phenotypic spectrum between the two forms.17,18

In autosomal recessive GTP-CH 1 deficiency, levels of monoamine neurotransmitter metabolites in the CSF and of pterins in the urine are reduced (Figures 3 and 4). Compound heterozygous or homozygous mutations in GCH1 provide genetic confirmation of the diagnosis. If genetic tests are inconclusive, measurement of residual GTP-CH 1 activity in fibroblasts might be helpful (Figure 4).18

Treatment for autosomal recessive GTP-CH 1 deficiency includes BH4 supplementation, but BH4 monotherapy cannot fully restore monoamine neurotransmitter synthesis, so levodopa and 5-hydroxytryptophan therapy is also required (Table 1).47

6-pyruvoyl tetrahydropterin synthase deficiency

PTPS deficiency is caused by mutations in PTS and occurs at its highest frequency in Asian populations. The phenotype ranges from mild disease (asymptomatic at treatment initiation) to severe neurological syndromes. Mutations that preserve greater enzyme function result in milder phenotypes. Neonatal patients are frequently small for gestational age and have hypotonia, microcephaly and poor suck. Associated movement disorders include hypokinesia, rigidity, chorea, dystonia and oculogyric crisis. Severe disease is associated with learning disabilities, epilepsy and psychiatric symptoms.7

Detection of hyperphenylalaninaemia with neonatal DBS screening enables early diagnosis of PTPS deficiency. CSF levels of HVA and 5-HIAA are usually both low, but can be normal. CSF levels of biopterin are low (Figure 3), and urine levels of neopterin are high (Figure 4). Treatment usually involves BH4, levodopa and 5-hydroxytryptophan supplementation (Table 1), but dopamine agonists, anticholinergics and benzodiazepines are also commonly used.52,53

Sepiapterin reductase deficiency

Sepiapterin reductase deficiency is an under-recognized autosomal recessive, levodopa-responsive disorder of pterin synthesis that results from mutations in SPR. The largest published series (which included 43 patients)
### Table: Neurotransmitter profiles, metabolite profiles and other diagnostic investigations in neurotransmitter disorders

<table>
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<th>Blood</th>
<th>Urine</th>
<th>Enzyme assays</th>
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<th>Clinical response</th>
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<tbody>
<tr>
<td></td>
<td>HVA</td>
<td>Phynyalanine⁴</td>
<td>Total biopterin</td>
<td>Fibroblast</td>
<td>Single gene testing</td>
<td>Trial of levodopa</td>
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<td></td>
<td>5-HIAA</td>
<td>Phenyalanine loading⁴</td>
<td>Neopterin</td>
<td>Blood</td>
<td>Microarray</td>
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<td></td>
<td>HVA:5-HIAA</td>
<td>Prolactin</td>
<td>HVA</td>
<td>Enzyme assays</td>
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<td></td>
<td>BH2</td>
<td>Dopamine*</td>
<td>5-OMD</td>
<td>Fibroblast</td>
<td>Microarray</td>
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<td></td>
<td>BH4</td>
<td>Noradrenaline*</td>
<td>Vanillylactic acid</td>
<td>Fibroblast</td>
<td>Microarray</td>
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<td></td>
<td>Sepiapterin</td>
<td>Adrenaline*</td>
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<td>Fibroblast</td>
<td>Microarray</td>
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<td></td>
<td>5-MTHF</td>
<td>Serotonin*</td>
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<td>Fibroblast</td>
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<td></td>
<td>Vitamin B6</td>
<td>Dried blood spot</td>
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<td>MHPG</td>
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<td>3-OMD</td>
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<td></td>
<td>Neopterin</td>
<td>Phe</td>
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<td>Fibroblast</td>
<td>Microarray</td>
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<td></td>
<td>HVA:creatinine</td>
<td>5-HIAA</td>
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<td>Fibroblast</td>
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<td>3-OMD</td>
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<td></td>
<td>Vanillylactic acid</td>
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**Key diagnostic tests**
- HVA: homovanillic acid
- 5-HIAA: 5-hydroxyindoleacetic acid
- 5-MTHF: 5-methyltetrahydrofolate
- AADC: aromatic l-amino acid decarboxylase
- BH2: dihydrobiopterin
- BH4: dihydropteridine reductase
- DHPR: dihydropteridine reductase
- DAT: dopamine transporter
- GTP-CH 1: GTP cyclohydrolase 1
- MHPG: 3-methoxy-4-hydroxyphenylglycol
- Phe: phenylalanine
- PITX3: pituitary homeobox 3
- PNPO: pyridoxamine 5'-phosphate oxygenase
- PTPS: 6-pyruvyl tetrahydropterin synthase

**A Abnormal, ↑ High, ↓ Low**

*Sample handling requires snap freezing. *Measured in either a dried blood spot or the plasma. ¹Phenylalanine:tyrosine ratio measured at 1, 2, 4 and 6 h after loading. ²Prolactin might not always be increased. Abbreviations: 3-OMD, 3-orthomethyldopa; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HTP, 5-hydroxytryptophan; 5-MTHF, 5-methyltetrahydrofolate; AADC, aromatic l-amino acid decarboxylase; BH2, dihydrobioptrin; DAT, dopamine transporter; DHPR, dihydropteridine reductase; GTP-CH 1, GTP cyclohydrolase 1; HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol; Phe, phenylalanine; PITX3, pituitary homeobox 3; PNPO, pyridoxamine 5'-phosphate oxygenase; PTPS, 6-pyruvyl tetrahydropterin synthase.
Clinical characteristics

Mild learning difficulties, hyperactivity, sleep disturbance, X-linked developmental delay, episodic hypotonia, hypotonia, hypokinesia, rigidity, chorea, dystonia, bradykinesia, rigidity, oculogyric crisis, levodopa responsiveness.

Management

Bulbar dysfunction, dyskinesia, tremor, dystonia, Droxidopa (100–600 μg/kg daily) 41,43,52

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical characteristics</th>
<th>Management*</th>
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<tr>
<td>Autosomal dominant GTP-CH 1 deficiency (Segawa syndrome)</td>
<td>Dopa-responsive dystonia, diurnal variation, levodopa responsiveness; mimic of spastic diplegic cerebral palsy and hereditary spastic paraparesis</td>
<td>Levodopa, initial dose 0.5–1.0 mg/kg daily, gradually increased to up to 5.0 mg/kg daily (&lt;3.0 mg/kg daily is often sufficient) 29,36</td>
</tr>
<tr>
<td>Autosomal recessive GTP-CH 1 deficiency</td>
<td>Truncal hypotonia, dystonia, seizures, developmental delay, levodopa responsiveness</td>
<td>BH4 1–10 mg/kg daily, 27 levodopa 1–10 mg/kg daily, 27,37 5-HTP 1–8 mg/kg daily 27</td>
</tr>
<tr>
<td>PTPS deficiency</td>
<td>Hypotonia, hypokinesia, rigidity, chorea, dystonia, oculogyric crisis, levodopa responsiveness</td>
<td>BH4 1–12 mg/kg daily, 21,25 levodopa 4–18 mg/kg daily, 25 5-HTP 1–10 mg/kg daily, 25 dopamine agonists and MAO inhibitors to avoid dopamine-related on–off phenomena 21,41,52,53</td>
</tr>
<tr>
<td>Sepiapterin reductase deficiency</td>
<td>Axial hypotonia, dystonia, oculogyric crisis, diurnal fluctuation, cerebral palsy-like presentation, levodopa responsiveness</td>
<td>Levodopa 0.5–2.0 mg/kg daily, 27,56,57 5-HTP 1–6 mg/kg daily, 27,56,57 seleagine 0.03–2.00 mg/kg daily 27</td>
</tr>
<tr>
<td>DHPR deficiency</td>
<td>Bulbar dysfunction, dyskinesia, tremor, dystonia, choreoathetosis, levodopa responsiveness</td>
<td>Levodopa 5–13 mg/kg daily, 61 5-HTP 3–11 mg/kg daily, 61 calcium folinate (folic acid) 15 mg daily, dopamine agonists and MAO inhibitors to avoid dopamine-related on–off phenomena 22</td>
</tr>
<tr>
<td>Pterin-4 α-carboxylamine dehydratase deficiency</td>
<td>Hypotonia or no symptoms, transient hyperphenylalaninaemia</td>
<td>Screen for hypomagnesaemia and onset of diabetes in adolescence</td>
</tr>
<tr>
<td>Tyrosine hydroxylase deficiency</td>
<td>Type A: Parkinsonism–dystonia, hypokinesia or bradykinesia, rigidity, diurnal variation; mimic of neuromuscular disorders and hypokinetic–rigid syndrome</td>
<td>Type A: levodopa 3–10 mg/kg daily, 16 trial of amantidine 4–6 mg/kg daily if levodopa-induced dyskinesia does not respond to a reduction in levodopa dose 29</td>
</tr>
<tr>
<td>Type B: Complex encephalopathy, focal or generalized dystonia with crises, severe parkinsonism, hypotonia, oculogyric crisis, tremor, ptosis, hypersalivation, autonomic dysfunction, levodopa responsiveness</td>
<td>Type B: levodopa &lt;0.5–2.0 mg/kg daily, 16 trial of amantidine 4–6 mg/kg daily if levodopa-induced dyskinesia does not respond to a reduction in levodopa dose 29</td>
<td></td>
</tr>
<tr>
<td>AADC deficiency</td>
<td>Hypotonia, oculogyric crisis, hypokinesia, chorea, dystonia, bulbar dysfunction, fasting hypoglycaemia</td>
<td>Pyridoxine 20–160 mg/kg daily, 29,71,79 calcium folinate (folic acid) 15 mg daily, dopamine agonists (rotigotine patch 0.17–0.25 mg/kg daily), 29 bromocriptine 0.013–4.000 mg/kg daily, pergolide 0.006–0.750 mg/kg daily, pramipexole 5 μg/kg daily in three doses, increased to 35 μg/kg daily in three doses, ropinirole 0.25 mg daily, increased by 0.25 mg every 3 days to 0.5–4 mg daily, selegeline 0.03–2.00 mg/kg daily, 10,79 trihexyphenidyl 1–12 mg daily (titrated slowly; much higher doses often tolerated, but monitoring for adverse effects is essential), benzotropine 1–4 mg/kg daily, clonidine 0.1–3.0 mg/kg daily (initial test dose recommended, higher doses used with caution owing to antihypertensive action), benzodiazepines</td>
</tr>
<tr>
<td>PNP0 deficiency</td>
<td>Severe drug-resistant neonatal-onset epileptic encephalopathy, in utero seizure onset, premature birth</td>
<td>Pyridoxal 5’-phosphate 30–50 mg/kg daily 40</td>
</tr>
<tr>
<td>PITX3 deletion</td>
<td>Mild learning difficulties, hyperactivity, sleep disturbance, distinctive facial features, hypoplastic middle fifth phalanges</td>
<td>Levodopa 1.0–2.5 mg/kg daily 49</td>
</tr>
<tr>
<td>MAO A or B deficiency</td>
<td>X-linked developmental delay, episodic hypotonia, learning difficulties, stereotypies and self-injurious behaviour, epicantthic folds</td>
<td>Consider dietary restriction of foods rich in tyramine phenylethylamine, m-tyramine and n-tyramine (cheese, chocolate, cocoa) 29</td>
</tr>
<tr>
<td>Dopamine β-hydroxylase deficiency</td>
<td>Ptosis, orthostatic hypotension, exercise intolerance</td>
<td>Droxidopa (100–600 mg daily in adults, with gradual titration) 103</td>
</tr>
<tr>
<td>Brain dopamine–serotonin vesicular transport disease</td>
<td>Axial hypotonia, oculogyric crisis, parkinsonism, tremor, facial dyskinesia, ptosis, bulbar dysfunction, sleep disturbance</td>
<td>Initial treatment with pramipexole 0.01–0.02 mg/kg daily in two doses (dose can be doubled according to gait dystonia and tolerability), trihexyphenidyl 0.2 mg/kg daily in two doses (increase slowly according to response) 48</td>
</tr>
<tr>
<td>Dopamine transporter deficiency syndrome</td>
<td>Feeding difficulties, irritability, axial hypotonia, dyskinnesia with progressive dystonia–parkinsonism, mimic of dyskinetic cerebral palsy; later onset with juvenile parkinsonism–dystonia; complete absence of dopamine uptake on DAT scan</td>
<td>Pramipexole 5 μg/kg daily in three doses, increased to 35 μg/kg daily in three doses, ropinirole 0.25 mg daily, increased by 0.25 mg every 3 days up to 0.5–4 mg daily 48</td>
</tr>
</tbody>
</table>

*Drug treatments are mainly based on reported clinical experience. Where citations are not provided for doses, the quoted doses are recommendations from the British National Formulary for children, 2014 edition. Levodopa is normally administered in combination with carbidopa. Abbreviations: 5-HTP, 5-hydroxytryptophan; AADC, aromatic L-amino acid decarboxylase; BH4, tetrahydrobiopterin; DHPR, dihydropterin reductase; GTP-CH 1, GTP cyclohydrolase 1; MAO, monoamine oxidase; PITX3, pituitary homeobox 3; PNP0, pyridoxine 5’-phosphate oxidase; PTPS, 6-pyruvoyl tetrahydrobiopterin synthase.

Table 1 | Clinical characteristics and management of primary monoamine neurotransmitter disorders

identified considerable delays in diagnosis owing to frequent misdiagnosis as cerebral palsy. Early disease in children manifests as an abnormal upward gaze, paroxysmal stiffening, and axial and/or limb hypotonia. Core features of the disease as it evolves include axial hypotonia, oculogyric crises, weakness, dystonia with diurnal fluctuation, and motor and language developmental delay. Head and limb resting tremor that
is inhibited by touch or spontaneous movement has also been reported.55 Parkinsonian features, sleep disorders, behavioural difficulties and psychiatric symptoms are common.56 The majority of patients have some degree of learning disability: only 8% have normal cognitive abilities.27,57 CSF levels of HVA and 5-HIAA are low in sepiapterin reductase deficiency, whereas total biopterin, BH2 and sepiapterin levels are high (Figure 3). Plasma phenylalanine levels and urine pterin levels are normal, but the phenylalanine loading test is abnormal (Figure 4).23 Sepiapterin reductase activity in fibroblasts is low.

In most patients with sepiapterin reductase deficiency, the condition is dopa-responsive.28 Some patients develop levodopa-related dyskinesia, so a low starting dose, followed by slow incrementation is recommended. Most patients require combination treatment with levodopa, 5-hydroxytryptophan and BH4; monoamine oxidase inhibitors are often also needed for management of movement disorders (Table 1).26 The benefits added by 5-hydroxytryptophan are unclear, but are thought to include modest improvements in cognition, movement disorders and sleeping patterns.26 Nevertheless, most patients retain a degree of cognitive and motor morbidity in the long term.27

**BH4 regeneration**

*Dihydropteridine reductase deficiency*

DHPR deficiency is the most severe pterin defect.15 The condition is usually identified by the detection of hyperphenylalaninaemia with newborn DBS screening; early diagnosis using this strategy is important because 40% of infants with DHPR deficiency are asymptomatic, but good clinical outcomes are associated with early treatment.15 DHPR deficiency manifests with bulbar dysfunction, feeding difficulty, hypersalivation, microcephaly and developmental delay.15 Associated movement disorders include limb hypertonia with truncal hypotonia, dyskinesia, tremor, dystonia and choreathetosis.15 Learning disabilities and seizures are also common.

DHPR deficiency leads to low CSF levels of HVA, 5-HIAA and methylethydrofolate, high levels of BH2, and high or normal levels of biopterin (Figure 3). Low DHPR activity measured with DBS screening supports the diagnosis, which is confirmed by the identification of mutations in QDPR.

Treatment of DHPR deficiency involves levodopa and 5-hydroxytryptophan (Table 1).15 Use of BH4 therapy is controversial despite the fact that the condition is a BH4 disorder, as it might increase levels of 7,8-DHPR, leading to uncoupling of neuronal nitric oxide synthase, consequent production of superoxides, and associated neurotoxicity.55 BH4 therapy could also have the undesired effect of inhibiting aromatic L-amino acid hydroxylase.59 Oral calcium folinate is routinely administered in DHPR deficiency (Table 1), as the enzyme has an important role in the maintenance of cerebral folate.59 Some severely affected children require phenylalanine dietary restriction to normalize phenylalanine levels and prevent phenylalanine-associated neurotoxicity.15

**Pterin-4α-carbinolamine dehydratase deficiency**

Pterin-4α-carbinolamine dehydratase (PCD) is necessary for BH4 regeneration after phenylalanine hydroxylation. PCD deficiency, which results from mutations in *PCBD1*, leads to mild hyperphenylalaninaemia, detectable with DBS screening, and high urine levels of 7-biotin. The CSF neurotransmitter profile is normal. PCD deficiency can present as transient hypertonia, but some patients are asymptomatic.60 The mild hyperphenylalaninaemia usually resolves on normal diet.

Discoveries of novel mutations in *PCBD1* indicate that patients with mild neonatal hyperphenylalaninaemia should be screened for diabetes mellitus and hypomagnesaemia in clinical follow-up. A novel deletion in *PCBD1* has been proposed as a cause of diabetes, as PCD is a dimerization cofactor for the hepatocyte nuclear factor transcription factors, which are important in liver and pancreas development and function.61 Similarly, a novel homozygous deletion in *PCBD1* results in a premature stop codon that abolishes the transcription factor binding and enzymatic functions of PCD, a process that is thought to cause hypomagnesaemia and diabetes.62 Re-evaluation of patients with mild neonatal hyperphenylalaninaemia owing to mutations in *PCBD1* identified three patients who developed diabetes during puberty, indicating early β-cell failure.63

**Impaired dopamine synthesis and regulation**

*Tyrosine hydroxylase deficiency*

Tyrosine hydroxylase catalyses the rate-limiting step in dopamine synthesis. Analysis of the largest cohort of patients with tyrosine hydroxylase deficiency studied to date (36 patients) identified two clinical phenotypes: Type A and Type B. Type A (69%) presents during infancy or childhood with hypokinetic rigid syndrome and dystonia. Type B (31%) presents in neonates or during early infancy as complex encephalopathy.64 Diurnal variation of symptoms is frequently observed in both phenotypes.64 Oculogryric crises, ptosis, hypersalivation, tremor, focal or generalized dystonia with crises, and autonomic disturbance are associated with the condition.16 The majority of patients also have nonprogressive learning disabilities.16 Approximately 50% of patients with tyrosine hydroxylase deficiency have hyperprolactinaemia, and this abnormality is rarely associated with galactorrhoea.16,64 By 3 months of age, patients with Type B deficiency exhibit severe parkinsonism, hypotonia and cognitive impairment.16 Reports of intermediate phenotypes indicate a disease continuum between Type A and Type B.29 Atypical clinical presentations include disease onset in later childhood, presentation with abnormal gait, early onset spastic paraplegia, and dopa-responsive myoclonus-dystonia.65-67

CSF levels of HVA are low in tyrosine hydroxylase deficiency, whereas levels of 5-HIAA are normal: the HVA:5-HIAA ratio is usually < 1 (normal range 1–4). CSF levels of synaptic proteins also seem to be abnormal in tyrosine hydroxylase deficiency.68 In 10 patients with tyrosine hydroxylase deficiency, concentrations of the dopamine transporter (DAT), dopamine D2 receptor and...
VMAT2 were higher than in age-matched healthy controls. Treatment with levodopa increased levels of the dopamine D2 receptor and HVA in a patient with Type B disease; by contrast, levels of the dopamine D2 receptor were reduced in two patients with Type A disease. Quantification of synaptic proteins in the CSF might provide further insight into neurotransmitter disorders and increase the possibility of personalized treatment.

Type A tyrosine hydroxylase deficiency responds well to treatment with levodopa (Table 1). In Type B disease, initial doses of levodopa should be low and titrated with caution (Table 1). The response to levodopa alone varies, and adjunct therapy with anticholinergics and/or dopamine agonists is often required to manage dystonia (Table 1). Doses of 5–10 mg/kg daily can be well tolerated in all phenotypes but some patients with tyrosine hydroxylase deficiency experience intolerable dyskinesia, even at low doses. This sensitivity might be caused by supersensitivity of striatal dopamine D1 and D2 receptors that results from chronic dopamine deficiency throughout development, or by excessive excitation of glutamatergic corticostriatal neurons. Levodopa-related dyskinesia can, therefore, be improved by decreasing the dose of levodopa, titrating the dose more slowly, or administering the N-methyl-D-aspartic acid receptor blocker amantadine to attenuate glutamatergic drive (Table 1).

Aromatic L-amino acid decarboxylase deficiency

AADC mediates decarboxylation of levodopa and 5-hydroxytryptophan to produce dopamine and serotonin, and requires pyridoxal 5'-phosphate as a cofactor (Figure 2). AADC deficiency owing to mutations in DDC has been reported in >100 patients. One third of these patients have a common founder mutation that was identified in patients from Taiwan and South China.

AADC deficiency can present at any age but is usually diagnosed in early childhood. Prominent clinical features include hypotonia (95%), oculogyric crisis (86%) and developmental delay (63%), and patients commonly present with ptosis. Congenital myasthenia gravis and other neuromuscular disorders are suspected in many patients before diagnosis. Approximately 50% of patients present with movement disorders (hypokinesia, chorea, dystonia, ballismus, dyskinesia, tremor, myoclonus), bulbar dysfunction (feeding and communication difficulties) and sleep disturbance. Patients also experience autonomic dysfunction that manifests as excessive sweating, temperature instability, nasal congestion, hypersalivation, hypotension, impaired stress responses and irritability. Fasting hypoglycaemia with autonomic dysfunction has also been reported, so monitoring of blood sugar levels is advisable when patients with AADC deficiency are required to fast. Milder phenotypes have been reported, in which initial symptoms are similar to myasthenia but evolve to become dystonia–parkinsonism in adulthood. These reports suggest that childhood symptoms can change with age, and AADC deficiency should also be considered for presentations of juvenile or early-onset parkinsonism.

In AADC deficiency, CSF levels of HVA, 5-HIAA and MHPG are low, and levels of 5-hydroxytryptophan, levodopa and 3-OMD are high (Figure 3). Urine levels of catecholamine metabolites (vanillylactate, 3-OMD) are high, and plasma AADC activity is low or entirely absent (Figure 4). Neuroimaging of patients with the condition reveals nonspecific features, including cerebral atrophy, white matter abnormalities and thinning of the corpus callosum.

Studies published in 2014 and 2015 have used novel techniques to detect AADC deficiency. The first study detected high levels of 3-OMD in patients with AADC deficiency by using DBS screening, indicating that this approach could be used as a presymptomatic screening tool. The second detected AADC deficiency with a mass spectrometry platform that enables parallel testing for hundreds of metabolites in a single plasma specimen. This approach revealed markedly elevated levels of 3-OMD in a boy who presented with developmental delay and hypotonia. Such techniques could be developed for future diagnostic use.

Levodopa is not routinely used in the treatment of AADC deficiency because the deficiency prevents conversion of levodopa to dopamine and further increases accumulation of 3-OMD, which depletes S-adenosylmethionine. However, when three siblings who had a homozygous DDC point mutation were treated with levodopa and pyridoxal 5'-phosphate, dystonia improved, though behavioural problems persisted. Molecular modelling and functional characterization of this point mutation suggested that it impairs binding of the AADC enzyme to its cofactor pyridoxal 5'-phosphate, resulting in loss of enzyme activity.

Treatment of AADC deficiency usually involves a combination of pyridoxine or pyridoxal 5'-phosphate, folic acid, monoamine oxidase (MAO) inhibitors and dopamine agonists (Table 1), although responses are variable and often disappointing: only 19% of patients report satisfactory treatment. For most patients, pyridoxine or pyridoxal 5'-phosphate with calcium folinate is usually initiated first, followed by the addition, as needed, of a monoamine inhibitor and dopamine agonist, and then other adjunct therapies such as trihexyphenidyl. Pyridoxine is intended to boost residual AADC activity after its conversion to pyridoxal 5'-phosphate. Pyridoxine elicits no clinical response, but can increase CSF levels of HVA and plasma levels of serotonin. No clinical consensus has been reached as to whether the administration of pyridoxine or pyridoxal 5'-phosphate is more effective, but pyridoxine seems to be better tolerated. Patients with AADC deficiency are given calcium folinate because they are at risk of cerebral folate deficiency. This risk results from the conversion of high levels of levodopa to 3-OMD, leading to depletion of S-adenosylmethionine, which is required for 5-methyltetrahydrofolate production. Dopamine agonists, such as bromocriptine, pramipexole and ropinirole, have variable effects on motor function, although rotigotine, which acts on dopamine D1–D5 receptors and has additional serotonergic and noradrenergic effects, has
been used with some success.86 Transdermal rotigotine patches are increasingly used to prevent the pharmacological peaks and troughs that occur with enteral administration of dopamine agonists (Table 1).71 The variable success of pharmacotherapy for AADC deficiency has driven translational research into gene therapy (see Novel therapeutics below).

Pyridoxine 5′-phosphate oxidase deficiency
PNPO catalyses production of pyridoxal 5′-phosphate. PNPO deficiency therefore leads to reduced synthesis and recycling of pyridoxal 5′-phosphate, resulting in reduced AADC activity and, consequently, impaired dopamine and serotonin synthesis.87

PNPO deficiency presents as a severe pharmacoresistant neonatal epileptic encephalopathy, often accompanied by a history of in utero seizures and premature birth.88 PNPO deficiency should be suspected if CSF levels of pyridoxal 5′-phosphate are low. CSF glycine, taurine, histidine and threonine might also be raised.89 The CSF neurotransmitter profile might be similar to that in AADC deficiency (Figure 3).89 If so, measuring plasma AADC activity is recommended to exclude AADC deficiency. If enzyme activity is normal, sequencing of the PNPO gene should be considered.89

If PNPO deficiency is suspected, treatment with pyridoxal 5′-phosphate should be trialled, and if the condition is genetically confirmed, then long-term treatment is used to reduce the seizure burden (Table 1).90 Pyridoxal 5′-phosphate treatment is associated with a risk of prolonged apnoea,90 so appropriate cardiorespiratory monitoring and precautionary support should be available to patients during treatment.

Pituitary homeobox 3 mutation
Recent studies have revealed a novel neurotransmitter disorder that results from mutation of PITX3, which encodes pituitary homeobox 3. This protein is a transcription factor involved in the translation of TH, which encodes tyrosine hydroxylase. Pituitary homeobox 3 is, therefore, involved in dopamine regulation.91 A deletion at chromosome 10q24.32, which encompasses PITX3, was identified in a 17-year-old male with mild learning difficulties, hyperactivity, behavioural problems and sleep disturbance.92 He had distinctive physical features of a high forehead, open mouth, synophrys, a short, broad nose and hypoplastic middle phalanges of his fifth digits.92 His CSF levels of HVA and 5-HIAA and biotin were low, and levodopa was absent. Treatment with levodopa led to improved behaviour, attention and sleep.92

Prior to publication of the case study above, the effects of Pitx3 mutations had been studied in mice. Pitx3−/− mice have selective loss of dopaminergic neurons in the substantia nigra and ventral tegmental area, leading to markedly reduced dopamine levels in the nigrostriatal pathway and dorsal striatum.92 The mice exhibit aberrant striatum-dependent cognition and nigrostriatal pathway sensorimotor deficits.92,93 Treatment of these mice with levodopa, dopamine, or dopamine agonists normalizes sensorimotor function.92,93 In future, whole-exome sequencing will undoubtedly identify more patients with PITX3 mutations and improve our understanding of this novel neurotransmitter disorder.

Dopamine metabolism deficits
Monoamine oxidase deletion syndrome
MAO A and B catalyse the oxidative deamination of dopamine to produce HVA and of serotonin to produce 5-HIAA (Figure 2). The MAOA and MAOB genes lie in opposite orientations at Xp11.23, and share 70% sequence homology.94 Individuals with MAO B deficiency are asymptomatic, whereas individuals with MAO A deficiency have borderline intellectual deficiency and impaired impulse control.94 Individuals with deficiency of both MAOs have mental retardation, episodic hypotonia, stereotypy and self-injurious behaviour. Levels of serotonin in the CSF and blood are high, whereas levels of dopamine-related deaminated metabolites are low (Figures 3 and 4).95 CSF levels of 5-HIAA are very low or undetectable.95

The NBD gene, deletion of which causes Norrie disease, is adjacent to MAOA and MAOB, and reports of dual MAO deletion often include NBD deletion. Patients with NBD deletions in addition to MAO deletion often exhibit features of Norrie disease, such as retinal dysplasia and congenital visual impairment.96 A report published in 2010, however, described two brothers with a 240kb deletion that encompassed exons 2–15 of MAOA and complete deletion of MAOB, without deletion of NBD.97 These individuals presented with severe developmental delay, mental retardation, seizures, and stereotypes.97 Both had hypotonia in infancy, worsening episodic hypotonia that resembled seizures, and mild facial dysmorphism that included epicanthal folds and long eyelashes.97 The older brother experienced recurrent screaming episodes with self-injurious behaviour, and died unexpectedly at 5 years of age. The younger brother experienced episodes of restlessness that were followed by hypotonia and loss of consciousness. At 15 years of age, he was ambulant, but ran clumsily and communicated with only single words and sign language. Subsequently, three more boys with MAOA and MOAB deletions and similar clinical phenotypes have been identified.95,98 Neuroimaging and electroencephalograms in all these patients were normal.95,97,98

Patients with MAO A and/or MAO B deficiency might also be at high risk of cardiovascular complications in response to excessive dietary intake of tyramine and phenylethylamine (foods based on cheese and cocoa beans). These compounds can act as sympathomimetics, and high levels can lead to severe hypertension, intracerebral haemorrhage, cardiac arrhythmias and cardiac failure.99 One boy in adolescence experienced a sudden collapse and required intensive care support after ingesting high amounts of phenylethylamine.99 This boy’s obligate carrier grandmother had a stroke after ingesting large quantities of tyramine.99 MAO A and MAO B deactivates phenylethylamine, m-tyramine, and p-tyramine,99 and people with deficiency of both MAOs are up to 4-fold more sensitive to intravenous tyramine than are those who have only MAO A deficiency.99 Dietary regulation of
phenylethylamine and tyramine intake might, therefore, reduce cardiovascular risk in these individuals.\textsuperscript{72}

Evidence from mouse studies indicates that \textit{MAOA–MAOB} deletion also affects proliferation of neural stem cells. In double-knockout mice, such proliferation is decreased from late gestation into adulthood.\textsuperscript{100} Levels of monoamines, particularly serotonin, are high in these mice, and the animals exhibit anxiety-like behaviour in adulthood.

**Dopamine \(\beta\)-hydroxylase deficiency**

Synthesis of noradrenaline from dopamine is catalysed by dopamine \(\beta\)-hydroxylase (DBH; Figure 2). DBH deficiency is a rare autosomal recessive condition that is caused by homozygous or compound heterozygous mutations in \textit{DBH} and affects autonomic function. The condition presents in childhood, typically with ptosis, hypotension and fatigability.\textsuperscript{101} By early adulthood, symptoms include profound orthostatic hypotension, reduced exercise tolerance, ptosis, nasal congestion and presyncopal symptoms (dizziness, blurred vision, dyspnoea, nuchal discomfort and chest pain).\textsuperscript{101} A study of a Dutch cohort of eight patients identified that the severe orthostatic hypotension in children with DBH deficiency frequently led to a misdiagnosis of epilepsy.\textsuperscript{102}

Biochemical hallmarks of DBH deficiency include minimal levels or absence of noradrenaline and adrenaline in the plasma, and 5–10-fold elevated plasma levels of dopamine.\textsuperscript{33} The normal response to infusion of tyramine—an increase in plasma levels of noradrenaline—is absent in DBH deficiency, and an increase in plasma levels of dopamine is seen instead, owing to limited conversion of tyramine to noradrenaline and upregulation of tyrosine hydroxylase (Figure 4).\textsuperscript{33} Hypomagnesaemia and mild anaemia have also been associated with DBH deficiency.\textsuperscript{33}

DBH deficiency is treated with droxidopa, which is converted directly into noradrenaline by AADC, thereby bypassing the requirement for DBH.\textsuperscript{103}

**Disrupted dopamine and serotonin transport**

**Brain dopamine–serotonin vesicular transport**

Brain dopamine–serotonin transport is a transportopathy caused by mutations in \textit{SLC18A2}, which encodes VMAT2 (Figure 2).\textsuperscript{22} VMAT2 facilitates dopamine and serotonin loading into synaptic vesicles for their transportation to the cell membrane and subsequent release.\textsuperscript{104} A homozygous loss-of-function \textit{SLC18A2} mutation has been identified in a single consanguineous family in which eight individuals were affected.\textsuperscript{22} The affected individuals presented in childhood with developmental delay, axial hypotonia and oculogyric crises. Bulbar dysfunction, ptosis, hypomimia, facial dyskinesia, tremor, ataxia and parkinsonian shuffling gait developed in adolescence. Psychiatric and autonomic features, including temperature instability, sweating, postural hypotension, depression and sleep disturbance, were observed in the index patient.\textsuperscript{22} Neither neuroimaging nor CSF neurotransmitter analysis (available for only one individual) revealed abnormalities. Urine levels of HVA and 5-HIAA were high, and levels of adrenaline and dopamine were low (Figure 4).\textsuperscript{22}

Initial treatment with levodopa caused worsening of dystonia and chorea.\textsuperscript{32} A subsequent trial of pramipexole, however, resulted in complete and sustained amelioration of motor symptoms and restoration of ambulation in some individuals. Adverse effects of hyperactivity and weight loss were observed, but tolerable (Table 1).\textsuperscript{45}

**Dopamine transporter deficiency syndrome**

DTDS, which was first reported in 2009, was the first monoamine transportopathy to be described. This autosomal recessive condition is caused by mutations in \textit{SLC6A3}, which encodes the dopamine transporter (Figure 2).\textsuperscript{20,21,32} Loss-of-function mutations lead to defective presynaptic uptake of dopamine that results in accumulation of dopamine in the synaptic cleft. This process underlies the CSF neurotransmitter profile that is characteristic of DTDS: high levels of HVA, normal levels of 5-HIAA and an HVA:5-HIAA ratio >5 (Figure 4).\textsuperscript{20,21}

DTDS presents in early infancy with feeding difficulties, irritability, axial hypotonia, a progressive hyperkinetic movement disorder and abnormal eye movements.\textsuperscript{20,21} During childhood, bradykinesia, hypomimia, rigidity and resting tremor predominate.\textsuperscript{20,22} As a result, DTDS is frequently misdiagnosed as dyskinetic cerebral palsy.\textsuperscript{21,32,105} MRI detects only subtle, nonspecific abnormalities if any,\textsuperscript{21} but \textsuperscript{123}I imaging (DaTscan\textsuperscript{®} [GE Healthcare, UK]) reveals complete loss of dopamine transporter activity in basal nuclei.\textsuperscript{21}

Early phenotype–genotype observations suggest that later-onset disease is associated with increased residual DAT activity.\textsuperscript{32,106} The phenotypic spectrum of DTDS is expanding: in 2014, juvenile parkinsonism\textsuperscript{32} and early-onset parkinsonism with ADHD were identified as novel DTDS phenotypes.\textsuperscript{107} As a result, DTDS is increasingly being considered as a differential diagnosis not only for cerebral palsy, but also juvenile parkinsonism.\textsuperscript{32,107,108} Currently available therapeutic agents are of little benefit in DTDS:\textsuperscript{32,107} levodopa and dopamine agonists have been used, but only a limited response was seen in a minority of patients (Table 1).\textsuperscript{21,32,107}

**Secondary neurotransmitter abnormalities**

Abnormal neurotransmitter profiles—defined as changes in the levels of monoamine, pterin, folate or pyridoxal 5′-phosphate metabolites in relation to age-related reference values—can occur in neurological conditions other than primary neurotransmitter disorders (Box 2).\textsuperscript{108–114} Most studies of these secondary neurotransmitter disorders have separated them into those associated with abnormal levels of HVA,\textsuperscript{106,109–112} or with abnormal levels of 5-HIAA (selective serotonin deficiency).\textsuperscript{113–115} In these conditions, disruption of monoamine metabolism might be secondary to dopaminergic and serotoninergic tract degeneration or defective monoamine metabolism.\textsuperscript{106,116}

**HVA disturbances**

A cohort study of 1,388 patients with neurological disorders identified abnormal CSF levels of HVA in epileptic...
encephalopathies (26.4%), pontocerebellar hypoplasia (4.3%), Rett syndrome (4.3%), leukodystrophies (6.8%), neuropsychiatric conditions (4.2%) and mitochondrial diseases (10.2%). Patients with low levels of HVA and symptoms of dopamine deficiency (that is, a movement disorder) can be given a trial of levodopa or dopamine agonists to determine whether they have any clinical benefit.

**A mimic of tyrosine hydroxylase deficiency**

A severe form of hypokinetic–rigid syndrome in infancy has been reported as a clinical and biochemical mimic of tyrosine hydroxylase deficiency. Children with the condition have a progressive neurological syndrome with low CSF levels of HVA. Some patients who presented with this tyrosine hydroxylase deficiency mimic were diagnosed with neurological conditions (such as mitochondrial diseases or hypoxic–ischaemic encephalopathy), but for many patients, no underlying cause has been identified.

In a cohort study of 15 children who presented with neonatal apnoea, axial hypotonia and limb rigidity with no identifiable aetiology, the patients developed features of infantile parkinsonism–dystonia with dyskinesia, and some exhibited oculogyric crisis. In all patients, CSF levels of HVA were low, whereas levels of all other markers were normal; the median HVA:5-HIAA ratio was 0.5 (range 0.17–2.6, normal range 1–4). Neuroimaging and other neurometabolic investigations were negative. Despite the phenotypic similarities to tyrosine hydroxylase deficiency, all patients were negative for mutations in TH and its promoter region. Ongoing levodopa treatment in nine of the 15 patients has produced a variable response, and the overall long-term survival in the cohort to date is 33%. In future, whole-exome sequencing is likely to identify genetic causes in a proportion of children with conditions that mimic tyrosine hydroxylase deficiency.

**Selective serotonin deficiency**

Selective serotonin deficiency comprises a heterogeneous group of neurological disorders that are associated with low levels of 5-HIAA but no abnormal levels of other neurotransmitter metabolites. In one study, low levels of 5-HIAA were reported in 19.3% of 606 paediatric patients with a wide variety of neurological disorders, including epileptic encephalopathy, movement disorders and autistic spectrum disorder. Another study reported a series of patients with idiopathic adult-onset dystonia accompanied by low levels of 5-HIAA. A further report identified paediatric patients with dystonia who had low levels of 5-HIAA (≥50% below age-matched reference ranges). This series included a subgroup of children with undetermined primary dystonic movement disorders, classified in this study as dopa-nonresponsive dystonia. Finally, one study identified secondary dystonia and low levels of 5-HIAA in children with hypoxic–ischaemic encephalopathy, white matter disease and neurodegenerative disorders. No genes within the serotonergic pathway have been associated with these unresolved cases of selective

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**Box 2** Secondary neurotransmitter disorders

<table>
<thead>
<tr>
<th>Low HVA and normal 5-HIAA</th>
<th>Low HVA and low 5-HIAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aicardi-Goutières syndrome</td>
<td>• Acute disseminated encephalomyelitis</td>
</tr>
<tr>
<td>• Allen–Herndon–Dudley syndrome</td>
<td>• Alexander disease</td>
</tr>
<tr>
<td>• CACNA1A mutations with ataxia</td>
<td>• Congenital infections</td>
</tr>
<tr>
<td>• Lesch–Nyhan syndrome</td>
<td>• Encephalitis</td>
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<tr>
<td>• Meningitis or encephalitis</td>
<td>• Guillain–Barre or Miller–Fisher syndrome</td>
</tr>
<tr>
<td>• Mitochondrial disorders</td>
<td>• Hypoxic ischaemic encephalopathy</td>
</tr>
<tr>
<td>• Nonketotic hyperglycaemia</td>
<td>• Methyltetrahydrofolate deficiency</td>
</tr>
<tr>
<td>• Perinatal hypoxic ischaemic encephalopathy</td>
<td>• Mitochondrial disorders</td>
</tr>
<tr>
<td>• Preterm-associated intraventricular haemorrhage</td>
<td>• Niemann–Pick type C</td>
</tr>
<tr>
<td>• Pontocerebellar hypoplasia type 2</td>
<td>• Nonketotic hyperglycaemia</td>
</tr>
<tr>
<td>• Rett syndrome</td>
<td>• Oligosaccharidosis</td>
</tr>
<tr>
<td>• Serine deficiency</td>
<td>• Pontocerebellar hypoplasia type 2</td>
</tr>
<tr>
<td>• Thiamine transporter 2 deficiency</td>
<td>• Rett syndrome</td>
</tr>
<tr>
<td>• Vanishing white matter disease</td>
<td>• Smith–Lesli–Optiz syndrome</td>
</tr>
<tr>
<td>• Urea cycle disorder</td>
<td>• Spontaneous periodic hypothermia and hyperhidrosis</td>
</tr>
<tr>
<td>• Tumour</td>
<td>• Stroke</td>
</tr>
<tr>
<td>• Urea cycle disorder</td>
<td>• Thalamic necrosis</td>
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<table>
<thead>
<tr>
<th>High HVA and normal 5-HIAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Angelman syndrome</td>
</tr>
<tr>
<td>• Hypoxic ischaemic encephalopathy</td>
</tr>
<tr>
<td>• Mitochondrial disease</td>
</tr>
<tr>
<td>• Meningitis or encephalitis</td>
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<tr>
<td>• Preterm-associated intraventricular haemorrhage</td>
</tr>
<tr>
<td>• Rett syndrome</td>
</tr>
<tr>
<td>• Stroke</td>
</tr>
<tr>
<td>• Urea cycle disorder</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Low 5-HIAA only</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Autism</td>
</tr>
<tr>
<td>• Idiopathic adult-onset dystonia</td>
</tr>
<tr>
<td>• Dopa non-responsive dystonia</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>High neopterin</th>
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<tbody>
<tr>
<td>• Early infantile epileptic encephalopathy</td>
</tr>
<tr>
<td>• Aicardi–Goutières syndrome (also reported with high neopterin and low methyltetrahydrofolate)</td>
</tr>
<tr>
<td>• Immune disorders and infection</td>
</tr>
<tr>
<td>• CNS infection</td>
</tr>
<tr>
<td>• HIV infection</td>
</tr>
<tr>
<td>• Low biopterin</td>
</tr>
<tr>
<td>• Early infantile epileptic encephalopathy</td>
</tr>
</tbody>
</table>

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid.
serotonin deficiency. Treatment with selective serotonin reuptake inhibitors or 5-hydroxytryptophan to increase serotonin levels could be considered for patients with selective serotonin deficiency and dopa nonresponsive dystonia.²

Immune-related disorders
The immunoinflammatory response to Th1-type IFN-γ and tumour necrosis factor-α can lead to an increase in neopterin levels. Neopterin is, therefore, a biomarker of activated cell-mediated immunity. Such immune-related elevation of neopterin levels is observed in encephalitis, HIV infection and neuroborreliosis.²⁰,²¹

The disorder Aicardi–Goutières syndrome (AGS) is associated with high CSF levels of neopterin. The disorder is genetic, with clinical features that can mimic in utero infection. Six genes are currently associated with AGS: TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1 and ADAR1.²²,²³,²⁴,²⁵ Features that indicate a diagnosis of genetic AGS include neurodevelopmental delay, chilblain-like skin lesions, early microcephaly, dystonia and sterile pyrexia. The condition also results in a classic triad of CSF biomarkers: high levels of IFN-α and neopterin, and chronic sterile CSF lymphocytosis.²²,²⁵ Levels of neopterin are highest at the earliest stages of disease and can normalize over time.²²,²⁵ Levels of HVA, 5-HIAA and 5-MTHF are usually normal,²⁵ although low levels of 5-MTHF have been reported.²⁶ Patients with AGS also have a markedly increased expression of interferon-stimulated genes, known as an interferon signature, that is often sustained. This signature reliably differentiates individuals with AGS from controls.²² Another distinctive feature of AGS is intracranial calcification—detectable with CT—in the basal ganglia (putamen, globus pallidus), thalamus and white matter, often accompanied by leukodystrophy that affects the frontotemporal regions and can be detected with MRI.²²

Management
Clinical interpretation of secondary monoamine neurotransmitter abnormalities and selection of therapeutic strategies require discussion with a neurometabolic laboratory and a neurotransmitter disease expert.²⁷ The benefits of levodopa in patients with low levels of HVA with a secondary cause (for example, mitochondrial disease) are unclear. In patients with symptomatic dopamine deficiency, a trial of levodopa is certainly warranted, and might improve motor function in some of these patients.²⁷ Treatment of central dopamine and/or serotonin deficiency should, therefore, be considered for symptomatic patients with secondary neurotransmitter abnormalities, even though long-term data about the effects of such intervention are currently lacking.

Future advances

Diagnostics
Whole exome and genome sequencing is likely to revolutionize diagnostic and therapeutic practice in monoamine neurotransmitter disorders. These techniques are becoming more economical and accessible, and will undoubtedly expand the clinical phenotypes that are associated with mutation of specific genes and improve the diagnosis of monoamine neurotransmitter disorders. For example, whole exome sequencing has identified syndromic intellectual disability as a new phenotype of AADC deficiency that is associated with Marfanoid features and facial dysmorphism.²⁸ New genetic neurotransmitter disorders are also likely to be identified with these techniques.

Research
The relationship between genotype and clinical phenotype is an important area of future study. Many monoamine neurotransmitter disorders encompass an expanding spectrum of phenotypes and atypical clinical presentations, and some genotype–phenotype correlation is seen in many of these disorders. Detailed delineation of the clinical and genetic features of newly identified patients with monoamine neurotransmitter abnormalities will further improve our understanding of these correlations.

Novel approaches to determine how mutations alter protein function might provide insight into disease mechanisms and provide the first steps towards personalized medicine. In AADC deficiency, studies are already underway to use bioinformatic, kinetic and spectroscopic analyses to characterize the molecular consequences of missense mutations so as to understand the disease mechanisms and responses to treatment in patients with different mutations.²⁹

To date, research into neurotransmitter disorders has been limited by the availability of robust neuronal models of disease. The development of in vitro models by the generation of dopaminergic neurons from patient-derived induced pluripotent stem cells has the potential to resolve this limitation.³⁰,³¹ Future research that makes use of cerebral organoids (three-dimensional organoid culture systems that derive from human pluripotent stem cells and develop discrete interdependent brain regions) could also increase our understanding of neurotransmitter systems in the context of wider brain neural networks.³²

Current animal models of neurotransmitter disorders were developed by using antisense morpholino oligonucleotides or homologous recombination. CRISPR–Cas9 gene editing is a more efficient method that enables rapid development of zebrafish and murine models.³³,³⁴ Use of this technique to develop models of known and novel monoamine neurotransmitter disorders will enable studies that increase our understanding of midbrain and dopaminergic neurogenesis and disease mechanisms, and will provide platforms for the development of novel therapeutics.

Therapies
Novel therapeutics are currently being developed for primary neurotransmitter disorders, particularly disorders that are refractory to current pharmacological strategies. Pseudoxon exclusion therapy with antisense morpholino oligonucleotides modifies gene expression

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by blocking translation of RNA. This technique was used to modulate splice mutations in the treatment of PTPS deficiency, and restored PTPS activity in fibroblast cell lines that were derived from three patients with intronic mutations that caused splicing defects.135

Clinical trials of gene therapy have been conducted in adult Parkinson disease with some success.135 In one trial, gene therapy with human AADC, delivered with the adeno-associated virus, was shown to be safe and resulted in stable expression of the gene and an improvement in parkinsonian rating scores that enabled a reduction in medication.136 In another trial, lentiviral-based gene therapy in Parkinson disease showed that TH, AADC and GCH delivery was safe and well tolerated, and improved motor scores.137 In another study, AADC delivery by stereotactic injection of adeno-associated virus to the putamina improved symptoms in four children with AADC deficiency, although initially caused dyskinesia.138 This gene therapy approach also increased putaminal uptake of 6-18F-fluoro-levodopa and increased CSF levels of dopamine and serotonin metabolites.139 Subsequent development of the Ddc61 mouse model of AADD deficiency has enabled evaluation of different gene therapy constructs, leading to the conclusion that neuronal-specific viral vectors are more effective than ubiquitous promoters in reducing dyskinesia.139 Nevertheless, the role that gene therapy can have in treatment of monoamine neurotransmitter disorders is undetermined, and further clinical trials are needed to learn more about the safety, efficacy and long-term benefits of this approach.

Conclusions

Childhood neurological disorders of monoamine dysregulation are an expanding group of genetic neurometabolic syndromes. Some of these conditions show a striking response to treatment, but the diagnosis and treatment of many remain challenging. In future research, rapid whole genome sequencing and biomarker discovery will identify novel neurotransmitter disorders and phenotypes, and will improve our understanding of genotype–phenotype correlation. Disease modelling with novel methods will reveal pathophysiological mechanisms and enable trials of novel small-molecules treatments. The generation of sophisticated neuronal models of disease from patient-derived induced pluripotent stem cells will improve our understanding of disease within the brain and provide a platform for high-throughput drug screening. The ability to rapidly develop transgenic animal models will also facilitate screening of new drug treatments and gene therapy. In combination, such novel therapies will form the basis of personalized medicine for these disorders.

Review criteria

We searched PubMed for English-language, full-text articles published between January 1990 and June 2015, using the search terms “monoamine” and “neurotransmitter”. Relevant articles were read and their references were screened for further relevant articles. Articles were included in the Review on the basis of research quality and current or potential impact on clinical practice.


56. Miller, A., Hyland, K., Milstein, S., Biaggioni, I. & Butler, I. J. Aromatic L-amino acid decarboxylase deficiency: clinical features,


**Acknowledgements**

M.A.K. is funded by a Wellcome Intermediate Clinical Fellowship (WT098524MA) and receives funding from the Rosetrees Trust and the Gracious Heart Charity Foundation. J.N. is funded by a Medical Research Council Clinical Research Training Fellowship (MR/K02342X/1). M.A.K. and J.N. are both funded by Great Ormond Street Hospital Children’s Charities. A.P. receives funding from Actelion to study undiagnosed neurodegenerative disorders, the NBIA Disorders Association and Child Brain Research. None of the authors received funding for the preparation of this manuscript.

**Author contributions**

J.N. wrote the first draft and provided substantial input into revision of the manuscript. A.P. prepared tables and figures and contributed to revision of the manuscript. S.J.H. contributed to the critique of the manuscript and figures. M.A.K. provided substantial input into the manuscript concept, design, content and revision of each draft.
Status dystonicus in childhood

Daniel E. Lumsden, Mary D. King, and Nicholas M. Allen

Purpose of review
Dystonia is a common paediatric neurological condition. At its most severe, dystonia may lead to life-threatening complications, a state termed status dystonicus. This review provides an update on the definition, causes, management and outcome of childhood status dystonicus.

Recent findings
High-quality studies in childhood status dystonicus are lacking, though an increasing number of case series have been published. Status dystonicus appears to occur more frequently in children compared with adults, with a clear precipitant identified in around two-thirds of cases. Although febrile illness remains the commonest trigger for status dystonicus, unplanned interruption to deep brain stimulation (DBS) is increasingly reported as a precipitant. In parallel with this, neurosurgical intervention for status dystonicus appears to have become more widely used, though optimum timing and patient selection remains unclear. In most cases, a multistaged approach is required; we propose an ‘ABCD’ approach – Addressing precipitants, Beginning supportive measures, Calibrating sedation and Dystonia specific medications.

Outcomes following status dystonicus appear to have slightly improved in recent years, potentially as a consequence of increasing use of DBS, though mortality has remained around 10%.

Summary
Future work is needed to inform evidence-based guidelines for the management of status dystonicus. One of many pressing questions is the precise indication, and timing of interventions such as DBS.

Keywords
dystonia, dystonic storm, life-threatening dystonia, rhabdomyolysis, status dystonicus

INTRODUCTION
Dystonia is a common presentation in the field of paediatric neurodisability. The term was first used by Oppenheim [1] over 100 years ago, describing a disorder of fluctuating tone affecting four children. Since then, understanding of dystonia has evolved, with changes in how the disorder is classified, categorized and conceptualized. Originally considered a disorder of basal ganglia function, it is now recognized that dystonia may arise because of disturbed function across much more widely distributed networks [2]. The most recent consensus update defines dystonia as ‘a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both’ [3,4]. Dystonia in children differs from that in adults in a number of ways: being most commonly a symptomatic condition, co-existing with other neurological abnormalities including spasticity, being expressed on the background of a developing brain, and presenting often as a sustained hypertonicity, rather than more intermittent involuntary movements [5–7]. This review will focus on providing an update on the more severe presentation of dystonia in childhood, ‘status dystonicus’.

DEFINING AND DELINEATING
Dystonia is usually a fluctuating state, where clinically the intensity varies over minutes, hours or days and there is paucity of readily available biomarkers for detection. At its most extreme, periods of ‘severe dystonia’ may be life-threatening but precisely defining when this state is entered remains

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Curr Opin Pediatr 2017, 29:674–682
DOI:10.1097/MOP.0000000000000556
challenging [8]. A variety of broadly overlapping terms continue to be used to encapsulate this state, including ‘status dystonicus’, ‘desperate dystonia’, ‘dystonic crisis’, ‘dystonic storm’, and ‘life-threatening dystonia’. Recently, status dystonicus appears to have become the most commonly used term, used for the remainder of this review, inclusive of all other terms used to describe extreme dystonia.

The criteria for status dystonicus proposed by Manji et al. [9], ‘increasingly frequent and severe episodes of generalized dystonia’, which necessitate urgent hospital admission, are frequently cited but are not well defined. Manji et al. note in their report that all cases in their series demonstrated one or more of the following life-threatening complications: bulbar weakness compromising upper airway patency with the risk of progressive impairment of respiratory function leading to the development of respiratory failure, exhaustion and pain and metabolic imbalances. Some authors have considered the presence of one or more of these additional features as necessary for the diagnosis of status dystonicus.

Recognising status dystonicus as the severe end of a continuum of deterioration, facilitates the application of a simplified Dystonia Severity Action Plan (DSAP) [10] ranging from grades 1 to 5 (Fig. 1) [11,12]. Although status dystonicus is the traditionally applied umbrella term encompassing ‘life-threatening dystonia’ and ‘dystonic storm’, along the DSAP scheme ‘status dystonicus/SD’ or ‘dystonic crisis’ as generally applied corresponds to DSAP grades 4 and 5. ‘Life-threatening dystonia’ corresponds to DSAP grade 5 and the term ‘dystonic storm’ has been described as the temporal evolution of status dystonicus, that is, a rapid deterioration in dystonia over hours or days to reach DSAP grades 4 and 5 [13]. Grade 3 DSAP is a pre-status dystonicus

KEY POINTS

- Status dystonicus represents the severe end of a deteriorating spectrum of dystonia severity.
- Status dystonicus appears to occur more commonly in children than in adults, with febrile illness the most commonly identified trigger, in established dystonia patients.
- Comprehensive prospective studies to guide status dystonicus management are lacking, but there is emerging consensus as to the need for a multipronged approach, which we summarize as: Addressing the precipitants, Beginning supportive measures, Calibrating sedation and Dystonia specific managements.
- Neurosurgical intervention appears to be more frequent in the management of status dystonicus, though debate remains as to the ideal candidates and optimal timing of DBS insertion, in the course of status dystonicus.

FIGURE 1. Screening for dystonia severity (grade) and action plan. Dystonia severity action plan (DSAP) (for established dystonia patients); Modified with permission from Lumsden et al. [10].
Differential Diagnosis
A number of neurological emergencies occur in children which may appear similar to status dystonicus, with significant overlap in clinical features (Table 1). More detailed comparison of these differential diagnoses is previously outlined [13,14].

Additional Hyperkinetic Elements in Children with Status Dystonicus
In children with dystonia, other elements of dyskinesia may often co-exist, for example, dystonia choreoathetosis in bilateral cerebral palsy, and as such, these movements may also be seen with dystonic spasms in status dystonicus. However, if the underlying cause of the movement disorder or context is poorly understood and dyskinetic (e.g. choreiform) movements are a prominent feature of the acute presentation, then alternative diagnoses to status dystonicus should be considered, for example, anti-N-methyl-D-aspartate receptor (NMDAR)-antibody encephalitis, Sydenham’s chorea, and so on (Table 1). The presence of dyskinetic movements with dystonic spasms in status dystonicus would not alter the management approach, but other disease-specific treatments may also be warranted (e.g. immunotherapy) for alternative diagnoses.

Causes and Triggers of Status Dystonicus
Robust prospective studies across a population of children at risk of developing status dystonicus are lacking. The most comprehensive systematic analysis of status dystonicus available was published by Fasano et al. [15], describing a total of 89 episodes of status dystonicus in 68 patients, 58.8% of whom were under age 15 years. Cases were categorized as ‘phasic’ if mainly characterized by rapid and repetitive dystonic movements, or ‘tonic’ (68.5%) if mainly characterized by sustained contractions and abnormal postures. A clear precipitant could be identified in 67.4% of episodes (of these 51.7% were because of infection, 30% drug adjustments, 6.7% surgical procedures, 5% metabolic disorders and 5% DBS failure or interruption). The aetiological classification of the underlying dystonia for these cases was secondary dystonia in 37.6% (59.3% of whom had cerebral palsy), primary dystonia 25.8% (TOR1A gene mutations in 18.8%) and heredodegenerative (27%). Updating this literature, we identified a further 44 episodes of status dystonicus reported in 41 cases (supplemental material, http://links.lww.com/MOP/A28), occurring in 35/44 (79.5%) occasions before age 16 years, with similar causes. For those episodes, wherever a precipitant could be identified [32/44 (72%)], fever or infection accounted for 17/32 (53.1%), interruption or discontinuation of DBS in 6/32 (18.8%), medication changes 3/32 (9.4%), surgery 2/32 (6%), followed by single episodes: metabolic disturbances, DBS surgery, abdominal discomfort and acute brain injury.

Management
The management of childhood status dystonicus is multifaceted but a basic approach can be summarized by ABCD (Fig. 2):

1. Address precipitants
2. Begin supportive care
3. Calibrate sedation
4. Dystonia specific medications

These elements are often considered and/or executed together. A robust evidence-base is lacking, and existing guidance is based upon expert opinion and personal experiences [13,14].

Addressing the precipitants
In two-thirds of cases, it is possible to identify a status dystonicus trigger, which should be treated whenever possible. A common trigger is infection. Although the commonest infective trigger, gastroenteritis, is usually viral, sepsis should be ruled out and empiric treatment should be considered in all cases, as well as searches for other sources. Pain may be a prominent trigger after surgery or trauma, and anticipatory strategies should be in place to prevent it (being mindful that opioid-based treatments may compound the respiratory depressant effect of sedative measures aimed at reducing dystonia). Gastrointestinal discomfort may also precipitate status dystonicus, for example, gastroesophageal reflux or constipation. Given the increasing reports of status dystonicus triggered by an unplanned discontinuation of neuromodulation with DBS or intrathecal baclofen (ITB), it is important that clinicians consider this possibility promptly. Medication changes are another important trigger. If withdrawal of a regular antidystonic medication has resulted in status dystonicus, then this medication should, wherever possible, be reinstated. Medica-
tions that have been identified as triggers in reported status dystonicus cases include pimozide and haloperidol, both dopamine-blocking agents (sometimes used to treat status dystonicus), and
<table>
<thead>
<tr>
<th>Neurological emergency</th>
<th>Motor or movement features</th>
<th>Time course onset</th>
<th>Trigger or cause</th>
<th>Rhabdomyolysis</th>
<th>Autonomic features</th>
<th>Reduced conscious level</th>
<th>Psychosis/delirium/agitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status dystonicus</td>
<td>Severe generalized dystonia, which may be accompanied by other hyperkinetism</td>
<td>Hours–days or longer depending on trigger</td>
<td>Identified in ~two-thirds of the cases</td>
<td>High risk</td>
<td>Not uncommon</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Neuroleptic malignant syndrome</td>
<td>Rigidity, often affecting lower limbs and trunk, with features of Parkinsonism</td>
<td>Days–weeks</td>
<td>Neuroleptics and some drugs for dystonia (e.g. pimozide)</td>
<td>High risk</td>
<td>Very prominent</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Serotonin syndrome</td>
<td>Prominent chorea/myoclonus, hypertreflexia, clonus, rigidity</td>
<td>Hours–days</td>
<td>Serotonergic agents – SSRIs, TCA, MAO-B, MDMA (ecstasy), triptans</td>
<td>High risk</td>
<td>Very prominent</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Malignant hyperthermia</td>
<td>Rigidity</td>
<td>Acute</td>
<td>Depolarising muscle relaxants or inhalational anaesthetic in genetically predisposed cases, for example RyR1 mutation</td>
<td>High risk</td>
<td>Prominent</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Paroxysmal autonomic instability with dystonia</td>
<td>Dystonic posturing, typically extensor involving trunk</td>
<td>Hours–days</td>
<td>Symptomatic brain injury – for example trauma, hypoxia, infection</td>
<td>Unusual</td>
<td>Very prominent (paroxysmal)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Intrathecal baclofen (ITB) withdrawal syndrome</td>
<td>Rebound in underlying movement disorder, with prominent spasticity and clonus</td>
<td>Acute, hours</td>
<td>ITB pump failure, catheter migration, disconnection</td>
<td>High risk</td>
<td>Prominent</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Acute dystonic reaction</td>
<td>Acute, typically focal dystonia</td>
<td>Acute</td>
<td>Medication ingestion, for example, cyclizine, haloperidol</td>
<td>Very unusual</td>
<td>Unusual</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sydenham’s chorea</td>
<td>Prominent chorea</td>
<td>Hours–days</td>
<td>Manifestation of rheumatic fever following beta-haemolytic streptococcal infection</td>
<td>Very unusual</td>
<td>Very unusual</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Autoimmune encephalitis</td>
<td>Dyskinesia, often prominent chorea, with buccolingual involvement</td>
<td>Days–weeks</td>
<td>Postinfectious, autoantibodies identified in a proportion</td>
<td>Unusual</td>
<td>Prominent</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Drug intoxication</td>
<td>Variable dyskinesia</td>
<td>Acute</td>
<td>Ingested drug</td>
<td>Very unusual</td>
<td>Not uncommon</td>
<td>Yes</td>
<td>Yes</td>
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MAO-Bi, monoamine oxidase type B inhibitors; RyR1, ryanodine receptor skeletal muscle mutations (most often); SSRIs, serotonin selective reuptake inhibitors; TCA, tricyclic antidepressants. Adapted from Allen et al. [14] and Termsarasab and Frucht [13*].
metoclopramide. In Wilson disease, chelation therapy with penicillamine, zinc sulphate or trientine have also been linked to the development of status dystonicus.

**Begin supportive measures**

Supportive measures are required to manage the direct consequences of the excessive muscle spasms, and the side-effects caused by many of the medication treatment strategies. Respiratory compromise may be because of pharyngeal or laryngeal spasm, compromised chest wall expansion from diaphragmatic or truncal dystonia or respiratory depression from exhaustion, potentiating by medication use. Early placement of a nasogastric tube may avoid potential aspiration and subsequent pneumonia, and provide a secure route for the delivery of enteral medications and feed or hydration. Intubation and ventilation may be required, but should not be considered mandatory. Tracheal tube per se may occasionally drive further dystonic posturing.

Cardiovascular instability may occur because of a combination of intravascular depletion because of dehydration, autonomic instability or cardiac arrhythmias because of metabolic disturbances. Intravenous (i.v.) fluids are generally required in the acute phase, particularly as gut motility may be impaired by a combination of dystonia and sedative or antidystonic medications. Metabolic/biochemical derangement may be a potentially life-threatening complication of status dystonicus, particularly whenever significant rhabdomyolysis has occurred (creatinine kinase more than 1000IU/l). Myoglobinamaemia may result in renal impairment and electrolyte disturbance, compounded by prerenal hypoperfusion because of dehydration. Renal impairment may necessitate haemodialysis or

**FIGURE 2.** Management of paediatric status dystonicus.

- Antibiotics if infection present
- Discontinue pharmacological precipitants
- Identify potential musculoskeletal drivers e.g. hip subluxation/dislocation
- Constipation disimpaction
- Gastro-oesophageal reflux treatment
- Review for DBS/ITB interruption/malfunction

**Begin Supportive Care**

- Urgent admission to HDU/PICU
- IV hydration
- Antipyretics +/- cooling blankets
- General comfort
- Analgesia and sleep promotion
- Monitoring – CK, electrolytes, liver profile
- Intensive supports
  - Intubation/Ventilation
  - Inotropes if required
  - Dialysis if required

**Calibrate Sedation**

- Chloral hydrate 30-100mg/kg 3-6 hourly
- Enteral clonidine, initially 3 micrograms/kg eight hourly
- IV clonidine, initially 0.5 micrograms/kg/hour
- IV Midazolam 30-100 micrograms/kg/hour
- General anaesthesia, e.g. propofol (some sedatives may treat dystonia e.g benzo diazepine/clonidine)

**Dystonia Specific Medications**

- Enteral (polytherapy if required)
  - Trihexyphenidyl
  - Gabapentin
  - Disopyramide
  - Tetrabenazine
  - Haloperidol
  - L-DOPA

**Address Precipitant**

- Antibiotics if infection present
- Discontinue pharmacological precipitants
- Identify potential musculoskeletal drivers e.g. hip subluxation/dislocation
- Constipation disimpaction
- Gastro-oesophageal reflux treatment

**Progression to neurosurgical intervention:**
- ITB (test dose prior to insertion)
- DBS
- Pallidotomy

**Refactory Cases**

- Urgent admission to HDU/PICU
- IV hydration
- Antipyretics +/- cooling blankets
- General comfort
- Analgesia and sleep promotion
- Monitoring – CK, electrolytes, liver profile
- Intensive supports
  - Intubation/Ventilation
  - Inotropes if required
  - Dialysis if required

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- Antibiotics if infection present
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- Chloral hydrate 30-100mg/kg 3-6 hourly
- Enteral clonidine, initially 3 micrograms/kg eight hourly
- IV clonidine, initially 0.5 micrograms/kg/hour
- IV Midazolam 30-100 micrograms/kg/hour
- General anaesthesia, e.g. propofol (some sedatives may treat dystonia e.g benzo diazepine/clonidine)
filtration. Repeated venipuncture may also drive dystonia and a balance is required between the benefits of close monitoring of biochemistry and the risk of creating further pro-dystonic drive.

**Calibrating sedation**

A cardinal feature of dystonia is remission with sleep [16]. A mainstay of the acute treatment of status dystonicus is the balanced administration of sedative medications to reduce dystonia severity and encouraging consistent periods of restful sleep. Caution is required with such medications because of the potential for respiratory depression. A hierarchical approach to temporizing agents is recommended.

Chloral hydrate may be administered enterally (30–100 mg/kg up to 3–4 hourly) to induce sleep. We tend to avoid ‘stat’ doses of benzodiazepines to avoid respiratory depression, reserving i.v. lorazepam or buccal midazolam for the uncommon situation whenever dystonic spasms result in acute airway compromise. In this situation however, anaesthetic airway management is essential.

Clonidine has emerged for the management of severe dystonia [17], and in status dystonicus can be used in combination with chloral hydrate. Administered enterally, a typical starting dose is 3 μg/kg per dose, initially 8-hourly but with escalation up to 3-hourly doses, delivering the equivalent of 3–5 μg/kg per hour in severe status dystonicus. Clonidine may also be delivered i.v., initially at a rate of 0.5 μg/kg per hour. Frequent review of vital signs including heart rate (resting tachycardia to measure discomfort, dehydration, etc.) and side-effects of medications, for example, hypotension, hypoventilation and sleep are important components of the monitoring strategy. Whenever status dystonicus is not controlled by a combination of chloral hydrate and clonidine, escalation to more aggressive sedation may be required, typically with continuous i.v. midazolam (30–100 μg/kg per hour) which may necessitate intubation and ventilation. If severe dystonic spasms continue, anaesthetic agents may be required (e.g. i.v. propofol or barbiturate infusions) and if dystonia remains refractory, nondepolarizing paralyzing agents are considered (avoiding depolarizing agents because of rhabdomyolysis risk).

**Dystonia-specific medications**

Temporizing measures providing sedation should be considered a ‘holding measure’ (for days or even weeks) whilst the trigger to the episode of status dystonicus is addressed, and a long-term management plan should be established. In some cases, it may be possible to abolish episodes of status dystonicus with temporizing measures alone, and then reduce these medications to a tolerable background level at which a good quality of life is achieved without excessive sedation.

More often, additional measures are required, and escalation wherever necessary should be deployed without delay. A large number of enteral medications have been described in the treatment of status dystonicus, including trihexyphenidyl, haloperidol, pimozide, tetrabenazine, gabapentin, baclofen, levodopa, as well as antiepileptics such as valproate, phenytoin and acetazolamide. In light of this, it is not possible to make an evidence-based recommendation as to which oral agent should be considered ‘first-line’. As status dystonicus generally occurs in children with a longstanding dystonic movement disorder, medication choices are likely to be dictated by pre-existing pharmacological management. In reported status dystonicus cases, first-line pharmacological therapies are rarely (~10%) effective alone [15]. This may represent a publication bias towards the most complex cases requiring interventions such as DBS whereas cases in which status dystonicus management was relatively straightforward are less likely to be published. In practice, early addition of specific antidystonia medications is important. Polypharmacy is often necessary and higher than regular starting doses, with rapid escalation over the early days and weeks, may be utilized, until benefit is achieved or unacceptable side-effects are observed.

For some disorders, certain medications should be avoided in status dystonicus. In aromatic l-amino acid decarboxylase (AADC)-deficiency dopamine antagonists and l-DOPA should be avoided [18]. In pantothenate kinase-associated neurodegeneration (PKAN), use of l-DOPA has been discouraged because of a lack of benefit, whereas use of medications with D2 antagonist activity (e.g. haloperidol or atypical antipsychotics) is discouraged because of the risk of tardive dyskinesia [19]. Precision therapies addressing the molecular basis of the expanding number of ‘genetic’ dystonias are currently lacking, but may emerge in future.

**OUTCOMES**

In the review by Fasano et al. [15] a multistage approach to management was described in most cases, with a surgical intervention (DBS, ‘lesioning’ or ITB) in 40.2% of status dystonicus episodes. A return to pre-status dystonicus baseline occurred in 36.8% of cases, an improvement compared with this baseline in 36.8% of cases, worsening in 16.2% and death in 10.3%. In our updated review, management of status dystonicus episodes was variably
documented but with similar outcomes: 43.2% improved compared with pre-status dystonicus baseline, 27.3% returned to baseline, 18.2% improved but not back to pre-status dystonicus baseline, and in 11.4%, status dystonicus resulted in death. A neurosurgical intervention was delivered in a higher proportion of cases in the updated review (65.9 versus 40.2% within the Fasano et al. [15] review).

**THE ROLE OF NEUROSURGICAL INTERVENTION**

An unresolved question is, at which point, if at all, in the course of status dystonicus should neurosurgical intervention be provided? Traditionally, neurosurgical intervention has been considered a last resort, but given the apparent benefit reported recently, it has been argued that early intervention

---

**FIGURE 3.** Sleep–wake chart. (a) Chart during status dystonicus and (b) post status dystonicus. Note this chart can be modified to annotate pharmacotherapy, as well as other bedside parameters and can be used at ward and intensive care level. Both patients were managed in ICU and ward.
be considered to avoid prolonged exposure to status dystonicus and related complications [13*,20*]. Recently it has been suggested that in ‘dystonic storm’ in the absence of a clear pharmacological precipitant, in conditions known to be highly responsive to DBS (e.g. DYT1), neurosurgical intervention should be considered within the first 24 h [13*]. In practice, this is likely to apply to few children as most presenting with status dystonicus have an underlying symptomatic or heredodegenerative dystonia, where outcome following DBS is less certain [21,22]. Even in the ‘ideal’ DBS candidate, the decision is not to be taken lightly. Complications to DBS surgery are not uncommon (infection of implanted devices is at least 10%) [23*], frequently resulting in the removal of the implanted equipment, and abrupt interruption of DBS delivery. Children reaching DSAP grade 5 are typically medically unstable or could be poorly nourished increasing surgical risks.

We suggest a measured approach to progression to DBS or ITB in children with status dystonicus, with early discussion regarding this option. Pharmacological management of status dystonicus should be attempted and the speed of progression to DBS should influence by the likelihood of benefit on an individual basis. Even in children with DYT1 dystonia, if status dystonicus can be controlled pharmacologically it may be possible to attain a period of prior medical stability to facilitate education on post-operative management of DBS, and clear goals.

Compared with DBS, the role of ITB in status dystonicus is less clear [24]. Similarly, a decision should be made on an individual basis. For example, ITB would generally be considered before DBS, in the child with significant spasticity with dystonia. Along the pathway of treatment, discussions regarding available therapeutic options should be balanced with prognosis, the underlying cause of the status dystonicus, goal setting and sometimes available resources.

**MONITORING DYSTONIA SEVERITY IN STATUS DYSTONICUS**

The objective measurement of dystonia severity is challenging, relying on lengthy scales that utilize standardized video-protocol formats [25–27]. These scales are impractical in the acute clinical setting, and are also limited by a significant ceiling effect. Application of the DSAP facilitates an objective, practice-based tracking of dystonia severity but once grades 4 and 5 have been reached, additional biomarkers related to medical complications or severity can serve as useful adjuncts. Rising creatine kinase levels are concerning as a marker of potential acute kidney injury whereas falling levels suggest a trend toward status dystonicus control. Similarly, transaminase measurements may also correlate with dystonia severity. Heart rate (tachycardia) will help recognize periods of control versus discomfort [28]. As the major aim of acute status dystonicus management is the establishment of regular sleep, sleep–wake charts should help determine trends and treatment responses (Fig. 3). Educating the family and multidisciplinary team regarding a potential lengthy in-patient admission, should facilitate expectations and consistency.

**UNANSWERED QUESTIONS**

Status dystonicus remains a poorly understood entity, with many questions requiring clarification through future research. Answering these questions will go some way towards generating a background of evidence upon which future guidelines may be based (Table 2).

### Table 2. Selected future questions

<table>
<thead>
<tr>
<th>Question</th>
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<tr>
<td>Robust, multicenter prospective studies to delineate the epidemiology and clinical characteristics</td>
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<tr>
<td>True incidence and prevalence of status dystonicus amongst children, and comparisons to adults</td>
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<td>Lifetime/annual risk for those with dystonia developing status dystonicus</td>
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<tr>
<td>Risk factors for status dystonicus, and to what extent can they be modified, for example, optimizing bone health in children with long-term neurodisability to reduce the risk of low-impact/occult fractures driving status dystonicus through pain</td>
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<tr>
<td>Can biomarkers be identified to quantify the risk of status dystonicus developing over a given time frame, or to objectively track both deterioration and recovery</td>
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<tr>
<td>The true impact of status dystonicus in childhood; long-term mortality, neurological and developmental morbidity, impact on participation</td>
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<tr>
<td>Optimal timing to initiate interventions</td>
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<tr>
<td>Are the optimal early interventions disorder specific, or generalizable across all patients regardless of the underlying cause</td>
</tr>
<tr>
<td>Role of DBS and other neurosurgical interventions for the management of status dystonicus and the cases for whom such interventions should be prioritized</td>
</tr>
<tr>
<td>Novel patient-specific, precision-based and molecular-based therapies for genetic dystonias</td>
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</tbody>
</table>
CONCLUSION
Status dystonicus represents the extreme end of a deteriorating dystonia spectrum, the mortality remaining unchanged (~10%) in recent years. Robust epidemiological studies are lacking, but the available evidence suggests that status dystonicus is more commonly encountered in children, particularly in those with acquired or heredodegenerative dystonia. In two-thirds of cases, a precipitant can be identified, most commonly infection. Over the last decade, interruption of DBS neuromodulation appears to have become a common status dystonicus trigger. In parallel, neurosurgical interventions for the treatment of status dystonia appear to have become more available (40.2–65.9% of reported cases). Management suggestions remain largely based upon expert opinion. The ABCD approach discussed, helps formulate individual management strategies.

Acknowledgements
None.

Financial support and sponsorship
None.

Conflicts of interest
There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as: ★ of special interest ☀ of outstanding interest

4. Lumsden DE, Gimeno H, Lin JP. Classification of dystonia in childhood. Parkinsonism Relat Disord 2016; 33:138–141. This article demonstrates an application in practice to a cohort of children and young people with dystonia of the most recent consensus update on dystonia classification.
Status dystonicus is a rare, but life-threatening movement disorder emergency. Urgent assessment is required and management is tailored to patient characteristics and complications. The use of dystonia action plans and early recognition of worsening dystonia may potentially facilitate intervention or prevent progression to status dystonicus. However, for established status dystonicus, rapidly deployed temporizing measures and different depths of sedation in an intensive care unit or high dependency unit are the most immediate and effective modalities for abating life-threatening spasms, while dystonia-specific treatment takes effect. If refractory status dystonicus persists despite orally active anti-dystonia drugs and unsuccessful weaning from sedative or anaesthetic agents, early consideration of intrathecal baclofen or deep brain stimulation is required. During status dystonicus, precise documentation of dystonia sites and severity as well as the baseline clinical state, using rating scales and videos is recommended. Further published descriptions of the clinical nature, timing of evolution, resolution, and epidemiology of status dystonicus are essential for a better collective understanding of this poorly understood heterogeneous emergency. In this review, we provide an overview of the clinical presentation and suggest a management approach for status dystonicus.
secondary (acquired) dystonias, and has a potentially worse outcome. The movements of status dystonicus may also overlap with additional, sometimes prominent, hyperkinesias such as choreoathetosis, which can make objective recognition complicated.6,8,9 Currently, there is no internationally agreed definition for status dystonicus. Criteria, including life-threatening complications proposed by Manji et al. are often cited.9 All patients in that case series developed one or more of the following: (1) bulbar weakness compromising airway patency, (2) progressive impairment of respiratory function leading to respiratory failure, (3) metabolic derangements, and (4) exhaustion and pain.

In practice, status dystonicus often occurs at the end of a continuum of worsening dystonia. Along such a continuum, a recently described simplified dystonia severity action plan may be useful to assess children at risk of status dystonicus and decide on the level of care required for management (see Fig. 1 and the supplementary material of Lumsden et al. for related clinical vignettes employed to validate the scale).10 In addition, the sites and severity of the dystonia may be documented using dystonia rating scales such as the Dyskinesia Impairment Scale for patients with cerebral palsy2 or the Burke-Fahn-Marsden rating scale.11 Video recordings are important for diagnosis and follow-up of treatment response. The baseline neurological state (coexisting spasticity, etc.) should also be recorded.

**Aetiology**

Status dystonicus usually emerges gradually after weeks or months in the patient with an underlying dystonia diagnosis. However, status dystonicus may also present during new onset dystonic disorders without previous or only mild dystonic movements.5,10,12,13 Some patients are prone to recurrent episodes. The acquired dystonias are the most common underlying dystonias leading to status dystonicus (38% of cases), CP being the most common individual secondary cause followed by the previously termed ‘heredodegenerative dystonias’ (particularly neurodegeneration with brain iron accumulation, Wilson disease, and mitochondrial disorders) and the ‘pure primary dystonias’.5 However, any form of dystonia has the potential to escalate into status dystonicus. If the cause of the underlying dystonia is not established, the history and clinical features will guide appropriate metabolic, genetic, neurophysiological, and neuroimaging investigations.

**Trigger factors**

Status dystonicus is often a triggered event. The main triggers include infection (particularly gastroenteritis with dehydration) and medication adjustment.7,13,14 Trauma, surgical procedures, anaesthesia, ‘metabolic disorder’ decompensation,15 stress,7 pain, gastro-oesophageal reflux disease, constipation, and puberty-related deterioration in CP are less commonly reported, but these conditions, as well as discomfort of any cause, should be considered.6 In about one-third of cases no obvious trigger is identified.5,13,14

**Complications and related investigations**

The muscle spasms or dystonic movements during status dystonicus give rise to complications that are at best painful and uncomfortable, and at worst life-threatening.5 Severe generalized muscle spasms may cause respiratory compromise and severe metabolic disturbances, particularly rhabdomyolysis and acute renal failure. The initial investigations are based on consideration of the complications, need for monitoring, supportive measures, and likely trigger factors.

Respiratory failure can be a function of dystonic bulbar spasms (pharyngeal, laryngeal), truncal-respiratory muscle spasm, diaphragm dystonia, generalized exhaustion, aspiration pneumonia, and indeed the need for highly sedative and relaxant cocktails of drugs used to control status dystonicus. Relevant respiratory investigations for these complications and triggers include chest X-ray, pulse oximetry, and blood gas monitoring, all of which should be part of the initial and ongoing supportive measures.

The biochemical derangements resulting from significant rhabdomyolysis23 include elevated creatine kinase (usually >5 times normal range, e.g. >1000 IU/L), myoglobinuria, myoglobinuria, electrolyte abnormalities, and acid-base disturbances. Muscle spasm-induced exothermia commonly leads to hyperpyrexia and dehydration. As well as clinically monitoring perfusion status (e.g. vital signs, capillary refill time, urine output), empirical tests for rhabdomyolysis and dehydration include renal chemistry, creatine kinase, blood gas analysis, urine and/or blood for myoglobin levels. A positive urine dipstick test for blood without red cells on microscopy is suggestive of recent muscle injury (over several hours).24 The creatine kinase may need to be repeated if negative at presentation because of a potential lag in elevation.

Further monitoring and investigations related to the management of rhabdomyolysis and renal failure (hypocalcaemia, hyperkalaemia, acidosis, haematological derangements, coagulopathy, pancreatic dysfunction, arrhythmias, compartment syndrome, and more) should involve appropriate medical, nephrology, and intensive care input.

**What this paper adds**

- An overview of status dystonicus and a practical approach to the management of status dystonicus and ‘pre-status dystonicus’.

Medications reported to trigger status dystonicus are important, particularly the dopamine-receptor blockers pimozide (exacerbated status dystonicus)16 and haloperidol as both can be used to treat dystonia and chorea.17 Metoclopramide8 can have the same effect. Clonazepam has been reported as a trigger (possibly coincidental) of status dystonicus.6,18,19 In Wilson disease the introduction of chelation therapy with penicillamine20,21 zinc sulphate,7 or trientine22 have also been implicated in status dystonicus. Clozapine treatment has been implicated,16 as well as withdrawal of lithium and tetrabenazine.6 Deep brain stimulation failure caused by hardware problems,5 intrathecal baclofen pump failure,12 as well as routine baclofen, and benzodiazepine withdrawal in general should be considered where relevant.
Status dystonicus patients are vulnerable to secondary complications such as dysphagia, anarthria, thrombosis, gastric bleeding, injuries, fractures, and sepsis. Some patients require tracheostomy or gastrostomy and some experience side effects or serious complications of treatment. A careful search for systemic or intracranial infection is usually warranted (appropriate septic screen).

**Differential diagnosis**
A variety of other emergency life-threatening movement disorders can have complications similar to status dystonicus (Table I). These include the neuroleptic malignant syndrome, serotonin syndrome, malignant hyperthermia, and intrathecal baclofen (ITB) withdrawal. Paroxysmal autonomic instability with dystonia is increasingly recognized in children. Acute dystonic reactions (usually to drugs) arise dramatically and may cause severe dystonic symptoms (e.g. oculogyric crisis, jaw opening, or closing dystonia). Rhabdomyolysis, muscle rigidity, and stiffness from other causes warrant consideration (Table I).

In severe status dystonicus the typical patient has an established or evolving dystonia disorder and develops worsening severe generalized dystonia, fever, dehydratio, or rhabdomyolysis and respiratory complications. Documentation of the precise evolution of the motor and other features of these disorders is crucial as some children have been diagnosed with neuroleptic malignant syndrome when drugs may not have been involved. ITB withdrawal can produce clinical features resembling status dystonicus.

**MANAGEMENT**

**‘Pre-status dystonicus’**
In some situations patient-specific management plans are used for known patients with brittle dystonia (characterized as difficult to manage or frequently requiring urgent medical attention) depending on the goals of treatment. In the case of patients who are hospitalized with severe subacute worsening dystonia or pre-dystonic crisis, lighter levels of sedation may be used alone or in combination to help achieve sleep, for example enteral chloral hydrate (30–100mg/kg, administered 3–6 hourly). In addition, oral, enteral or intravenous (IV) clonidine has a less sedating, non-respiratory depressant effect and may prove effective in achieving control or preventing breakthrough dystonia. Doses of 1–5µg/kg/dose may be administered three times daily, but may need to be offered every 3 hours (amounting up to 3,000µg per day in some cases with weights exceeding 70kg). Clonidine can be administered by continuous enteral infusion via NG tube or gastrostomy if necessary by calculating the total daily dose and dividing by 24 hours to deliver. Where the enteral route is unsuitable owing to vomiting, diarrhea, gastrointestinal bleeding or ileus, the equivalent doses may have to be administered as IV hourly infusion (doses of 0.25–2.0µg/kg/hr), with consideration of higher or bolus doses as tolerated (JP Lin, unpublished data). Clormethiazole (if available) or trimeprazine may also achieve lighter levels of sedation. Roubertie et al. also suggest effective use of intravenous amitriptyline for painful dystonic spasms. The addition or modification of other antidystonia agents according to the patient plan (e.g. trihexyphenidyl, gabapentin, or baclofen) should be considered. Benzodiazepines also may need to be considered. Although these practical suggestions may help prevent progression to status dystonicus and mostly represent lighter levels of sedation, very little has been published regarding these approaches. For status dystonicus, more prompt and aggressive treatment is often indicated.

**Established status dystonicus**
As status dystonicus is rarely reported, the evidence for treatment is derived from summation of case reports or series and is therefore empiric. Medical stabilization with supportive care is the initial priority. Figure 1 outlines a practical screening and management approach to status dystonicus.

**Stabilization and supportive measures**
In order to control an episode of status dystonicus as safely as possible, treatment should take place in the intensive care or high dependency unit. Immediate management of the complications is paramount. Depending on clinical indication (respiratory or systemic compromise, need for comfort or sedation), the initial stabilization measures often, but not always, involve intubation and mechanical ventilation. Intravenous fluid resuscitation, antibiotics, nutritional requirements (nasogastric or parenteral) and antipyretics should be provided early. Rhabdomyolysis requires specific therapy (e.g. intravenous fluids, urine alkalinization, dantrolene, neuromuscular paralysis, and/or dialysis in acute renal failure). Trigger factors and other complications should be prevented or identified and treated specifically. Other patient comfort and sleep promoting measures include appropriate positioning and minimal handling, and opioid analgesia may be required. A relatively long intensive care unit course should be anticipated for each presentation.

**Temporizing treatments**
Status dystonicus exerts its life-threatening effects precisely because sustained active muscle contraction leads to exhaustion and rhabdomyolysis. Depending on the clinical state and complications, an important initial measure is to help the child achieve some sleep without compromising respiration. Judicious use of a few doses of chloral hydrate (see Fig. 1) via nasogastric tube when oral medication is impossible to administer may enable sleep. Oral, enteral or intravenous clonidine (as in the case of pre-status dystonicus) should also be used because of its non-respiratory depressant advantages. In addition, rapid escalation of enteral doses of clonidine as high as 3–5µg/kg/hr (administered in 3-hourly bolus doses) have been tolerated successfully in several children with established status dystonicus, the dose being revised every 3 to 6 hours (JP Lin, unpublished data). If the enteral route is unsuitable, an IV clonidine infusion may be necessary to establish dystonia.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Motor features</th>
<th>Onset</th>
<th>Trigger/cause</th>
<th>Medical</th>
<th>Autonomic</th>
<th>Rhomboid/lysis</th>
<th>Respiratory</th>
<th>Mental</th>
<th>Other</th>
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</thead>
<tbody>
<tr>
<td>Status dystonicus</td>
<td>Severe generalized hypertonia</td>
<td>Common</td>
<td>Pruritis, paraesthesias,</td>
<td>Usually ok</td>
<td>Common</td>
<td>Respiratory compromise, bronchodilators, azathioprine</td>
<td>Respiratory compromise, bronchodilators, azathioprine</td>
<td>Usually ok</td>
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<td>Neuroleptic malignant syndrome</td>
<td>Neuro muscular excitability, hypotension, hypothermia,</td>
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<td>Serotonin syndrome</td>
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<td>Usually intra peritoneal</td>
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<td>Malignant hyperthermia</td>
<td>Malignant hyperthermia</td>
<td>Usually severe</td>
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<td>Paroxysmal acute dystonic reactions</td>
<td>Paroxysmal acute dystonic reactions</td>
<td>Acute (12-24h) or within days hours of drug trigger</td>
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<td>Acute dystonic reactions</td>
<td>Acute dystonic reactions</td>
<td>Immediately to hours after drug trigger</td>
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</table>
**Grade 1**
- Sits comfortably
- Regular sleep
- Stable on medication

**Grade 2**
- Irritable and cannot settle
- Posturing interferes with seating activities
- Can only tolerate lying despite baseline medication

**Grade 3**
- Can’t tolerate lying
- Sleep disturbed
- No signs of metabolic disturbance
- As in Grade 2

**Grade 4**
- Clinically as in Grade 3
- With metabolic disturbance: fever, dehydration, abnormal electrolytes, CK >1000 IU/L, myoglobinuria

**Grade 5**
- Severe generalized dystonia
- As per Grade 4 with full metabolic decompensation (metabolic, renal) or respiratory-cardiovascular compromise: organ support

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**Status dystonicus**

### 1. Supportive care
- Urgent admission
- HDU or ICU
- IV hydration
- Anti-pyretics
- Cooling blankets
- Analgesia
- Monitor (CK, renal, other parameters)
- Identify and treat triggers (e.g. IV antibiotics)
- General comfort and sleep
- Known patient: consider specific plan
- Intubate PRN

### 2. Temporizing measures
- Sedative hypnotic (sleep): 
  - e.g. enteral chloral hydrate 30 to 100 mg/kg q 3–6 hourly to achieve sleep
  - Invasive
  - Non-respiratory depressant: 
    - e.g. enteral or IV clonidine
    - Use higher than regular starting doses with use of high (bolus or continuous infusion) doses as tolerated (see Text for doses)
  - Sedative hypnotic (spasms): 
    - IV midazolam 30 to 100 µg/kg/hr (tolerance may develop quickly)
  - General anaesthesia: 
    - e.g. propofol 0.3 to 3 mg/kg/hr (monitoring for propofol infusion syndrome)
  - Paralytic agents: 
    - (non-depolarizing e.g. pancuronium)

### 3. Dystonia-specific
- Dystonia-specific oral agents (Status Dystonicus)
  - Trihexyphenidyl: slow increment as tolerated to maximum benefit.
  - Tetrabenazine: particularly total body dystonia where seating/sleeping difficult and child frequently distressed.
  - Enteral (or IV) clonidine: the least sedative dose possible.
  - Other: benzodiazepines, baclofen, tetrabenazine.

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**Figure 1:** Screening for dystonia severity (grade) and action plan with overview of the management of status dystonicus. DSAP, dystonia severity action plan (for established dystonia patients); GPi, Globus pallidus internus; ITB, intrathecal baclofen; DBS, deep brain stimulation; CK, creatine kinase; ICU, intensive care unit; HDU, high dependency unit; IV, intravenous. Modified with permission from Lumsden et al. and S. Frucht, Movement Disorder Emergencies: Diagnosis and Treatment (2nd edition, NY: Humana Press, 2011).
control (see ‘Pre-status dystonicus’ for dose considerations). In practice, if additional ‘as required’ medication is needed to settle a child, the background clonidine dose must be increased to achieve comfort, sleep and metabolic stability.

When more aggressive treatment is indicated, the precise approach depends on individual case severity and degree of complications.6,10,22,34 Stronger sedation and muscle relaxation or muscle paralysis are the measures most likely to achieve prompt resolution of the dystonic spasms.5,22 A benzodiazepine, i.e. continuous intravenous midazolam is usually chosen because of its muscle relaxant effect, rapid onset of action, and short half-life, and should be titrated efficiently to control dystonic spasms (see Fig. 1). For refractory spasms, anesthetic agents (propofol most often) followed by non-depolarizing muscle paralyzing agents (as depolarizing agents, e.g. suxamethonium, are associated with rhabdomyolysis) and barbiturates are then indicated.22

The duration of initial intubation and temporizing measures utilized are determined by periodic evaluation of the patient’s clinical response while specific antidystonia treatments are being concurrently considered. As ileus may be a serious complication of both status dystonicus and the polypharmacy used in its management, it is essential to keep the combination of drugs to a minimum, using a few drugs at optimal doses, often exceeding usual ranges but titrated against oxygen saturations, heart rate, and blood pressure. Also, it is essential to remember that facilitating regular periods of sleep is a safe and secure mechanism of managing status dystonicus that may need to be maintained for several weeks or possibly months allowing time to explore the underlying problems and management. Some degree of success may be claimed when the child’s heart rate dips slightly from baseline wakeful state during true sleep; a feature not obtained if the child is dystonic. Intermittent reductions of the sedative and anaesthetic agents administered should be attempted, as some patients develop dependence on, or tolerance of sedative medications. In others, the status dystonicus abates. Where success is achieved, initial attempts should be made to maintain the beneficial agents by appropriate routes of administration (e.g. oral, nasogastric, or gastrostomy clonidine, midazolam, and/or specific antidystonia drugs).13

**Dystonia-specific drugs**

Although clonidine and midazolam also have specific sometimes effective antidystonia properties, and may control an episode of status dystonicus, other specific oral antidystonia agents are also recommended. The variety of drugs used is broad with success in approximately 10% of cases only,3 but as they are non-invasive a trial of these agents should be considered in the first instance and before surgery. In our practice, we consider these medications once stabilization measures have been achieved and temporizing treatments described have been initiated and the response observed. The drugs reported to have most success are often used in combination and include an anticholinergic (trihexyphenidyl), a dopamine blocker (haloperidol or pimozide), and a catecholamine depleter (tetraabenazine) (Fig. 1).5,6,13,14,16,22

Many other oral drugs have been tried. In Wilson disease several patients with refractory status dystonicus were treated with gabapentin and significantly improved where other antidystonia drugs failed, so it should be used in this condition, and considered in other aetiologies.21 Other benzodiazepines (clonazepam, flurazepam, diazepam) have been used with11 and without success.7,36 Trials of oral baclofen,25 levodopa, or levodopa-carbidopa have also been suggested, leading to improvement in a few cases.6,7,37 Primary anticonvulsants including valproate, carbamazepine, primidone, phentoin,38 and acetazolamide6 have been used in various combinations, often with limited benefit. Benztrtopine, biperiden, lithium, bromocriptine,6,7 chlorpromazine, olanzapine,39 clozapine, and risperidone4 have also been used with mostly limited success. Many of the drugs used to treat dystonia can have significant side effects and some such as pimozide (e.g. cardiac side effects) may exacerbate status dystonicus (see ‘Trigger factors’).6,16,22 In such situations the drug should be discontinued.

As the response overall to orally active antidystonia drugs is reported to be poor, with significant risk to patients who develop dependence on sedative or anaesthetic agents and remain in refractory status dystonicus, more invasive step-up surgical therapies including ITB, deep brain stimulation (DBS), or pallidotomy, need to be considered early, once acute or active systemic infections have been clearly excluded or treated.

**Invasive therapies**

**Intrathecal baclofen.** Intrathecal baclofen has been tried in a small number (~10%) of patients with refractory status dystonicus with various reports of benefit,12–14,40,41 and failure.5,6,22,16,18,19,42 Some of these failures have been the result of complications36 or tolerance,38 which may potentially limit the use of ITB over long periods. ITB is not without other risks such as over-dosage, withdrawal syndrome, and commonly catheter migration or breakage, although it is considered less invasive than brain surgery.

**Deep brain stimulation.** Deep brain stimulation has been an effective treatment for status dystonicus in the majority of treated patients (approximately 25%).5,7–9,14,17,19,22,42–50 The globus pallidus interna (bilaterally) is the current anatomical site of choice for this surgical procedure. The effects of DBS were obvious and occurred usually within days or weeks; only occasionally did the effect take months. Although the evidence for DBS in status dystonicus is generated from case reports or series, DBS allowed many patients to become weaned from sedative and anaesthetic agents8 and in some improvement to baseline or beyond the level of their pre-morbid states.49 Further plausible evidence for DBS is suggested by device interruption (stimulation or battery), which provoked the appearance of
dystonic spasms, with resolution after switching stimulators back on or by device adjustments.9,42,45

Given the observed benefit of DBS, some authors feel that a rapid and aggressive approach is justified to avoid the longer-term complications of status dystonicus and serious morbidity or mortality.8 However, DBS is not without side effects. Operating on patients with status dystonicus is particularly challenging because of a higher rate of hardware (15%) and other serious complications in already compromised patients.9 Further challenges exist with urgent DBS surgery in children compared with adults, as a result of anatomical and developmental factors (although it has been used in a child as young as 5 years with status dystonicus).49

Where the globus pallidus interna was not an option (because of damage), the subthalamic nucleus may be targeted, as recently seen in a 4-year-old with severe methylmalonic academia and refractory dystonia.51 Thus, evaluation for DBS must be considered on an individual basis.

**Palidotomy and thalamotomy.** DBS has largely replaced pallidotomy, thalamotomy, and pallidothalamotomy for the treatment of dystonia. These ‘lesional’ procedures have been used in approximately 10 cases of status dystonicus with a variety of underlying dystonia disorders with variable outcomes. If DBS is not available, unilateral pallidotomy could be considered.5—7,14,36,37,42,52

**CONCLUSION**

Status dystonicus is a rare but life-threatening movement disorder emergency usually occurring in the context of various established dystonia disorders. Management should be tailored to individual patient characteristics and complications.5,49 The use of dystonia severity action plans aids the early recognition of worsening dystonia, and communication between health professionals, and may potentially facilitate intervention. For established status dystonicus, sedation in a high dependency or intensive care unit is the most immediate and effective intervention while exploring the specific or individual problems and management issues. The outcome of status dystonicus is variable and for the most part unpredictable. Mortality is reported at approximately 10%, recently suggested to be more common in males with a tonic phenotype and the heredodegenerative and secondary dystonias in which relapses are also more common.5 Some patients experience progressively worsening dystonia after status dystonicus, but this is not always so. Thankfully the majority of surviving cases gain either partial or complete recovery when compared with baseline neurological status and some improve beyond that.5 Further reports of the clinical nature and epidemiology of status dystonicus are essential for a better collective understanding of this poorly understood heterogeneous emergency.

**ACKNOWLEDGEMENTS**

We would like to thank the relevant authors for permission to modify aspects of their material to produce Figure 1.

**DISCLOSURES**

Dr Jean-Pierre Lin (JPL) has received honoraria for educational and consulting projects not related to this work from Medtronic Ltd and grants from Action Medical Research and the Dystonia Society UK. JPL is on the medical Advisory Boards of The Dystonia Society UK and Dystonia Europe and Chairs the British Paediatric Neurology Association Movement Disorders Special Interest Group (BPNAMDSIG). Prof. Tim Lynch has received honoraria from a number of companies not related to this work including Biogen, Lundbeck, Novartis, Solvay and unrestricted grant sponsorship for research from Bayer-Schering, Merck Serono, for the Dublin Neurological Institute from Elan and Sanofi-Aventis.

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