Dystonia

Introduction
Dystonia is a common movement disorder with a heterogenous clinical presentation. The fundamental clinical feature of the disorder is involuntary muscle spasm leading to the abnormal posture of the affected body part. An analysis of each patient who presents with dystonia in terms of age of onset, distribution of dystonia, and associated clinical features is invaluable in planning appropriate investigations, reaching the correct diagnosis and choosing effective treatment.

Is this dystonia?
Given the heterogenous clinical presentation of dystonia, this can sometimes be a difficult question to answer. Sustained muscle spasm leading to abnormal (but not usually fixed) posturing of the affected body part is the cardinal feature of dystonia. The spasms in dystonia are mobile, and this often leads to a slow writhing of the affected body part (athetosis). Co-contraction of agonist and antagonist muscles are the underlying reason for the abnormal posturing in dystonia, and this can be seen clinically, or more easily on simple EMG assessment of the affected body part. Tremor, often jerky and present only in particular postures, is commonly seen. Dystonia is often task or position specific, present only on writing for example, but not during other manual tasks. Patients with dystonia will often have sensory tricks or "geste antagoniste", where applying a sensory stimulus to a particular area will cause the abnormal posture to resolve.

Classifying dystonia – the essential division into primary and secondary dystonias
An outline of ways in which dystonia can be classified is given in table 1. Classifying by age at onset (below age 28, above age 28), distribution (focal, segmental, generalised) can be useful for planning investigations, and for picking out patients who present with unusual phenotypes (e.g. an adult presenting with generalised dystonia, which would be incompatible with typical primary dystonia). However, clinically the most useful division is classifying patients into those with "primary dystonia" – where dystonia is the only clinical sign (+/- tremor), and there is no neurodegeneration – and "secondary/heredodegenerative" dystonic conditions. Clinical features or "red flags" that should make one consider secondary dystonia rather than primary dystonia are listed in Table 2.

Dystonia-plus syndromes, a recent addition to the classification scheme, are idiopathic conditions where dystonia is present along with other clinical features e.g. myoclonus in myoclonus-dystonia, parkinsonism in dopa-responsive dystonia, but no neurodegeneration is evident.

Primary dystonia
In patients with primary dystonia, age at onset appears to be very important in determining the clinical phenotype. Young-onset dystonia (before the age of 28) is most commonly associated with limb onset dystonia followed by subsequent generalisation (although typically the neck is spared). About 70% of patients presenting in this way will carry the DYT1 gene mutation, a single GAG deletion in the DYT1 gene on chromosome 9. This condition has an autosomal dominant inheritance, but a very low phenotypic penetrance such that only 30-40% of gene carriers will ever develop dystonia, and in those that do, this will almost always happen before the age of 30. It is particularly important to diagnose this condition as deep brain stimulation of the internal segment of the globus pallidus (GPi, see below), appears to be a particularly effective treatment for such patients.

When dystonia appears in adult life, a focal distribution is commonly seen. These presentations, in order of frequency of occurrence include cervical dystonia (spasmodic torticollis), cranial dystonia (blepharospasm, Meige syndrome (blepharospasm and oromandibular dystonia)), writer's cramp, and other task specific dystonias. Cranio-cervical dystonia is commoner in women than men, with the opposite pattern seen in task-specific writing dystonias.

Dystonia-plus syndromes
Dopa-responsive dystonia (DRD), previously also called Segawa's disease, typically presents in childhood with limb dystonia, often with associated parkinsonism and sometimes spasticity. A diurnal fluctuation in symptom severity with a gradual worsening of symptoms throughout the day was said to be typical of the condition, but is present in only 60% of cases. This condition is usually due to mutations in the GTP cyclohydrolase 1 gene (GTPCH1), a rate limiting step in the production of dopamine from tyrosine. Although rare, it is of critical importance to the practising neurologist as it is entirely treatable by small doses of levodopa. This typically leads to complete resolution of symptoms which is sustained, without the development of long-term complications as seen in Parkinson's disease.

The condition can present with unusual phenotypes such as spastic diplegia, writer's cramp and other focal dystonias. In view of this, a trial of levodopa is strongly recommended in all those with young-onset dystonia especially as agenetic diagnosis is time consuming and not generally available. It is also important to differentiate patients with DRD from those with young-onset Parkinson's disease, many of whom will have limb dystonia in addition to Pakinsonism, and in whom the early use of levodopa is not recommended. A DAT SPECT scan (normal in DRD) can be useful in this regard. Other inherited defects of dopamine synthesis pathway, for example tyrosine hydroxylase deficiency, can also cause DRD, but usually as part of a more severe neurological syndrome.

Symptomatic dystonia
Dystonia is commonly seen following brain injury, for example perinatally (dystonic/athetoid cerebral palsy) or following stroke. In such patients a static deficit is

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Table 1: Different ways of classifying dystonia

By age at onset	By distribution	By aetiology
Young-onset dystonia) (< 28 years Adult-onset dystonia (> 28 years)	Focal Segmental Multifocal Hemidystonia Generalised	Primary (dystonia only +/- tremor; no neurodegeneration. Dystonia-plus syndromes - Dopa-responsive dystonia - Myoclonus dystonia Secondary - Symptomatic - Heredodegenerative Paroxysmal

commonly seen, although onset can be delayed for months or even years after injury, and late worsening of symptoms is sometimes seen.

Tardive dystonia is a common and disabling consequence of the long-term use of dopamine receptor blocking drugs. Although the newer "atypical" neuroleptic drugs appear to be safer with regard to this complication than older drugs, there are no entirely safe dopamine receptor blocking drugs (including drugs used for nausea such as metoclopramide).

Heredodegenerative dystonias – syndromic associations help guide appropriate investigation

Dystonia can be a feature of a wide range of neurodegenerative conditions, which can make selection and prioritisation of the appropriate investigations and reaching the correct diagnosis a difficult task. One aspect of such conditions that can be helpful, is that many have syndromic associations which can help guide the investigating clinician. For example peripheral neuropathy in association with dystonia would make one think of neuroacanthocytosis or metachromatic leukodystrophy as more likely diagnoses. Prominent ataxia would make one consider Wilson's disease or SCA3. Prominent bulbar involvement by dystonia would favour Neurodegeneration with Brain Iron accumulation (formerly known as Hallervorden-Spatz syndrome) or neuroacanthocytosis. A list of some of these conditions, with their associated clinical symptoms, is given in Table 3.

Investigation of dystonia

Following a careful history (in particular drug and family history) and examination, investigation of patients with dystonia should be tailored to the presentation of the patient, and in particular whether the picture is one of primary or secondary dystonia. Common clinical situations are of children/adolescents presenting with a primary focal or generalised dystonia, adults presenting with a primary focal dystonia, and the more extensive investigation of patients with presumed secondary dystonias. An outline of the investigations in these three situations is given in Table 4.

Table 2: Clinical features on history and examination suggestive of secondary dystonia

Clinical features on history and examination suggestive of secondary dystonia
Abnormal birth/perinatal history
Developmental delay
Seizures
Previous exposure to drugs e.g. dopamine receptor blockers
Continued progression of symptoms
Prominent bulbar involvement by dystonia
Unusual distribution of dystonia given age of onset (e.g. leg dystonia in an adult)
Unusual nature of dystonia (e.g. fixed dystonic postures)
Hemidystonia
Additional neurological symptoms (pyramidal signs, cerebellar signs, cognitive decline)
Other systems affected (e.g. organomegaly)

Treatment of dystonia

Drug treatment of dystonia is most appropriate in those with generalised/segmental dystonia for whom botulinum toxin (see below) would be unlikely to control the full extent of the dystonia. First line treatment is with anticholinergics such as trihexyphenydyl (Benzhexol/Artane). A slow introduction of the drug is very important to avoid side-effects, but some patients, in particular younger patients, can reach very high doses (100mg and above per day), with good effect. Clonazepam is particularly useful for the treatment of tremor, jerks and pain associated with dystonia. Other drugs which are sometimes useful include tetrabenazine, baclofen and even dopamine receptor blocking drugs. As mentioned above, all patients with young-onset dystonia should receive a trial of levodopa.

Botulinum toxin has revolutionised the treatment of patients with focal dystonia. Treatment is required every three-four months, and is expensive, but a 70-80% improvement in symptoms is common in most patients, particularly those with blepharospasm and cervical dystonia. Treatment of those with limb dystonia, in particular writer's cramp, is often more difficult and benefit can be inconsistent. Main side effects of treatment are excessive weakness of the treated muscle or spread of effect to nearby muscles (e.g. paralysis of pharyngeal muscles following sternomastoid injections). Immune-mediated resistance to botulinum toxin is seen in a small proportion of chronically treated patients, particularly those who receive high doses, "top-up" doses, or injections more frequently than every 12 weeks. An alternative toxin, botulinum toxin type B is available, but antibodies to the commonly used type A toxin can be cross-reactive with type B toxin, and in addition, a primary immune response to type B toxin can also occur. Botulinum toxin can be helpful for those with generalised dystonia where a particular functional problem can be linked to dystonia in a single or a small group of muscles.

Additional Web Content

For a case study on vertical gaze palsy, see www.acnr.co.uk/case%20report.htm

Table 3: Examples of some heredodegenerative causes of dystonia with associated neurological features.

Heredodegenerative Dystonias	Associated neurological features
Wilson's Disease	Kaiser-Fleischer rings, ataxia, cognitive decline
Neurodegeneration with Brain Iron accumulation (Hallervorden Spatz syndrome)	Retinal degeneration, pyramidal signs, oromandibular/ bulbar involvement
Neuroacanthocytosis	Peripheral neuropathy, oromandibular dystonia, epilepsy
Metachromatic Leukodystrophy	Peripheral neuropathy, frontal dementia
GM1/GM2 gangliosidosis	Cognitive decline
Glutaric acidemia	Cognitive decline
Huntington's disease	Cognitive decline, personality change, depression, supranuclear eye movement abnormalities
Niemann Pick type C	Vertical gaze palsy, cognitive decline
Ataxia telangectasia	Supranuclear eye movement abnormalities

Peripheral surgical treatment of dystonia has been used in the past to treat focal dystonias (e.g. cervical ramisectomy or selective peripheral denervation for cervical dystonia), and some benefit has been reported. Regrowth of sectioned nerves is often seen over time however, and with the advent of botulinum toxin, these treatments are now typically only considered for those with botulinum toxin resistant focal dystonia.

Both thalamotomy and pallidotomy have demonstrated effectiveness in the treatment of generalised dystonia, but both carry notable surgical risks. In recent years, deep brain stimulation of the GPi has gained favour as a successful treatment for generalised, and more recently focal dystonias. The operation itself carries less risk than lesion procedures, and results over the past 5 years or so have demonstrated a worthwhile and sustained benefit in many patients. This is most clearly the case for patients (mainly with generalised dystonia) who carry the DYT1 gene. Other patients with primary generalised and focal dystonias have also been reported to gain good benefit. Patients with secondary dystonia typically show a much less favourable response to DBS, and would need careful consideration before surgery was contemplated.

Table 4: List of investigations appropriate to three typical clinical scenarios. Investigation of secondary dystonia should be guided by syndromic associations (see Table 3).

Young-onset dystonia, clinically of primary type	Adult-onset dystonia clinically of primary type	Patients with dystonia where secondary dystonia considered
Copper studies, slit lamp to exclude Wilson's disease (NB liver biopsy remains gold standard)	Copper studies and slit lamp to exclude Wilson's disease if presentation under 50 years of age.	- MRI Imaging brain/spine (structural lesions, leukodystrophies, "eye of tiger" sign in NBIA (formerly known as Hallervorden Spatz syndrome) - Nerve conduction studies (neuroacanthocytosis, metachromatic leukodystrophy) -Copper studies, slit lamp, ?liver biopsy (Wilson's)
MRI brain	Consider MRI brain	- Huntington's disease gene test
DYT1 gene test	MRI spine if fixed/painful dystonia.	- White cell enzymes (GM1, GM2, metachromatic leukodystrophy)
Trial of levodopa	Paraspinal EMG, anti-GAD antibodies if painful axial muscle spasms to exclude stiff person syndrome	- Alphafetoprotein, immunoglobulins (ataxia telangiectasia) - Lactate/pyruvate, mitochondrial mutations, muscle biopsy (mitochondrial disease) - Fresh thick blood smear for acanthocytes (neuroacanthocytosis) - Plasma amino acids, Urine for organic acids, aminoacids, oligosaccharides (Glutaric academia, GM1, GM2) - Bone marrow biopsy / axillary skin biopsy (Niemann Pick C, Kufs) - Phenylalanine loading test CSF pterins assessments (DRD) - ERG, retinal examination , PANK2 gene test (positive in some cases of neurodegeneration with brain iron accumulation (Hallervorden Spatz syndrome)).

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Brain Tumour Information For Headstrong Kids

For the thousands of children who have a brain tumour, new multi-media information is now available. For the first time, children with brain tumours and their parents have collaborated with the Brain and Spine Foundation to produce Headstrong. Involving children in this way is a new approach to providing health information on brain disorders.

Headstrong helps children find out more about their illness, cope with their treatment and therefore lessen their anxiety. The first in a planned series of information services for children, it comprises a ring-bound folder for children aged seven to nine years old, a magazine-style publication for those aged 10–12 years, CD-Rom and a website.

But what makes Headstrong so different is that children have described their own experiences, hopes and fears in order that the information reflects what children and their parents say they need. The overall style of Headstrong has also been influenced by the children's views on the text and design. It has been developed by a panel of doctors specialising in cancer in children, experts from Great Ormond Street Hospital, hospital play specialists, experts in children's welfare, children's writers and graphic designers. "Headstrong is a highly skilled resource which helps children with brain tumours understand their condition while encouraging openness with their parents and carers," said Dr David Walker, consultant paediatric oncologist at the University of Nottingham.

"It was clear from our research that children and their parents were badly in need of information about brain tumours," said Ms Maggie Alexander, director of the Brain and Spine Foundation. "Our collaboration with children to develop health information for their own age group has not been done before. We were surprised and pleased by their terrific enthusiasm to help other children with a brain tumour and their parents or carers."

Using cartoons, illustrations and scenarios based on what the children had said in discussion groups, Headstrong explains what a brain tumour is, the symptoms, what a scan is, surgery, chemotherapy and radiotherapy as well as the recovery process. The facts are brought to life with the feelings and worries that children experience. Hannah, who had a brain tumour removed when she was just seven years old, tells the reader what it is like to lose her hair, whilst Joshua, 15, shows off his scar to his sister.

Around 350 children are diagnosed with a brain tumour each year and approximately 2,500 children between seven and 12 years old are living with one. "We believe that this project will also encourage children to have their say in decisions about their treatment. Everyone is different and children should be enabled to participate in managing their illness," said Ms Alexander.

Headstrong, which has been endorsed by the Centre for Health Information Quality, is being offered to specialist centres and hospitals where children are treated. Nurses, GPs, teachers and families will also find the information useful.

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