INTRODUCTION

Dystonia is a movement disorder that is characterised by abnormal postures of the affected body part. There are a number of features of these abnormal postures that make one suspect dystonia rather than another cause. First, these postures are not usually fixed, and as muscle activity shifts in intensity, the posture also changes. The slow writhing movements that can be caused by this phenomenon are known as athetosis. Second, the postures tend to be worsened, or indeed may only appear, when the affected body part is in a particular position, or when performing a particular task (e.g. writing). Third, patients will often find that if they touch the affected body part, the abnormal posture will resolve to a certain extent -- this is a “sensory trick” or “geste antagoniste”. Fourth, the postures are characterised by co-contraction of agonist and antagonist muscles. As well as abnormal postures, patients with dystonia may also develop a tremor, usually of the body part affected by dystonia. This tremor tends to be jerky, and, just like the abnormal postures, may be worsened or only appear when the limb is in a particular position or performing a particular task. Pain is not typically the predominant clinical feature in patients with dystonia, although it can occur, particularly in cervical dystonia.

HOW SHOULD ONE CLASSIFY DYSTONIA?

Dystonia can be classified in a number of ways (Table 1), but clinically the most useful classification system is the aetiological one. This divides dystonia into six main categories: primary dystonia, dystonia plus, secondary dystonia, heredodegenerative dystonia, paroxysmal dystonia and psychogenic dystonia. These are discussed in detail below, with the exception of paroxysmal and psychogenic dystonia. Readers are directed towards other sources (1-8) for discussion of these rare forms of dystonia.
The most useful clinical distinction to try to make when faced by a patient with dystonia is if the patient has primary dystonia or has a secondary/heredodegenerative dystonia. This fundamental distinction is of enormous benefit in guiding diagnosis, investigation and treatment.

PRIMARY DYSTONIA

In primary dystonia patients have dystonia as the only clinical feature with or without tremor. There should be no secondary cause evident, and brain imaging will be normal.

When deciding if a patient probably has primary dystonia, it is important to bear in mind that many patients with secondary and degenerative dystonia can present with dystonia as the only clinical feature, and indeed might have normal brain imaging initially. What can one do in this situation to help reach the conclusion that the patient does indeed have primary dystonia?

The key to answering this question is to think of the normal patterns of presentation of primary dystonia, and to ask oneself if the patient fits in with these. Primary dystonia has an anatomical distribution that very much depends on age at onset. Therefore, patients with young onset dystonia (<28 yrs) tend to have dystonia that starts in a limb, and then becomes generalised. This type of dystonia almost never affects the face and bulbar muscles. Patients who develop dystonia between the ages of 30 and 40 tend to develop focal dystonia of the hand (writer’s cramp) or other task-specific dystonias (e.g. musician’s dystonia). Patients who develop dystonia over the age of 40 (mostly in 50’s and 60’s) tend to develop focal dystonia of the cranio-cervical muscles e.g. cervical dystonia, laryngeal dystonia, oromandibular dystonia, blepharospasm, Meige syndrome (blepharospasm + oromandibular dystonia). Knowledge of these patterns is important in considering if the dystonia is indeed primary. For example, a 60 year old woman presenting with isolated foot dystonia, even if dystonia is her only clinical feature, would make one very suspicious that primary dystonia is not the cause, and other causes need to be considered. Apart from an unusual distribution of dystonia for age at onset, there are other “red flags” that should make one cautious about diagnosing primary dystonia, and these are listed in Table 2.

Young-onset primary dystonia is commonly caused by mutations in the DYT1 gene\(^9\). In such patients, a single GAG deletion in the DYT1 gene causes onset of dystonia in a limb which will then usually spread, typically over months to a year or so, to affect the rest of the body, but sparing the face and bulbar muscles\(^9\). A number of atypical phenotypes have also been described\(^9\). The gene is inherited in an autosomal dominant fashion, but
has very reduced clinical penetrance, so that only about 30% of mutation carriers will develop dystonia. In addition, this penetrance is age dependent, so that mutation carriers who pass the age of 30 without developing dystonia, almost never develop dystonia later in life. Mutation carriers who do not develop dystonia have a subnormal response to experimental techniques that cause plastic changes in the brain, in comparison to an excessive response to the same technique in mutation carriers with dystonia. This adds weight to the theory that susceptibility to undergo plastic change may be excessive in people with dystonia, and that this drives the development of abnormalities in the motor system. There is marked variability in the severity of DYT1 dystonia, with some patients just having mild focal dystonia, while others are severely disabled. The mutation is common in the Ashkenazi Jewish population due to a founder effect, but is seen in many other populations. Patients with DYT1 dystonia often respond extremely well to deep brain stimulation of the internal segment of the globus pallidus (see below). In patients with young-onset dystonia (<30 yrs) which is clinically of the primary type, a minimum set of investigations would include MRI brain imaging, copper studies, DYT1 gene testing and a trial of levodopa if appropriate (see below under dopa-responsive dystonia). One should always keep in mind that some secondary/degenerative forms of dystonia can present with dystonia as the only clinical feature and have normal imaging, therefore the clinician should be alert to the development of symptoms that are at odds with the diagnosis of primary dystonia (e.g. continued progression of symptoms), and investigate as appropriate.

Patients with clinically typical adult-onset primary dystonia often do not require extensive investigation. Copper studies are appropriate in patients under 60 years of age, and consideration should be given to a trial of levodopa in younger patients (see under dopa-responsive dystonia below). Again, development of symptoms that would be unusual for primary dystonia should always prompt a re-evaluation of the patient and appropriate further investigations.

Table 2. “Red flags” on history and examination that suggest the dystonia may not be primary

<table>
<thead>
<tr>
<th>Abnormal birth/perinatal history</th>
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<tr>
<td>Developmental delay</td>
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<tr>
<td>Seizures</td>
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<tr>
<td>Previous exposure to drugs e.g. dopamine receptor blockers</td>
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<tr>
<td>Continued progression of symptoms</td>
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<tr>
<td>Prominent bulbar involvement by dystonia</td>
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<tr>
<td>Unusual distribution of dystonia given age of onset (e.g. leg dystonia in an adult)</td>
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<td>Unusual nature of dystonia (e.g. fixed dystonic postures)</td>
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<tr>
<td>Hemidystonia</td>
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<td>Presence of another movement disorder (other than tremor)</td>
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<tr>
<td>Additional neurological symptoms (pyramidal signs, cerebellar signs, cognitive decline)</td>
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<tr>
<td>Other systems affected (e.g. organomegaly)</td>
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In patients with young-onset dystonia (<30 yrs) which is clinically of the primary type, a minimum set of investigations would include MRI brain imaging, copper studies, DYT1 gene testing and a trial of levodopa if appropriate (see below under dopa-responsive dystonia). One should always keep in mind that some secondary/degenerative forms of dystonia can present with dystonia as the only clinical feature and have normal imaging, therefore the clinician should be alert to the development of symptoms that are at odds with the diagnosis of primary dystonia (e.g. continued progression of symptoms), and investigate as appropriate.
DYSTONIA-PLUS SYNDROMES

Dystonia-plus syndromes are a group of three conditions where dystonia occurs with other symptoms and signs, but there is no neurodegeneration, and they are therefore somewhat different to the secondary/degenerative disorders discussed below.

Dopa-responsive dystonia

This is an autosomal dominant condition caused in about 80% of cases by mutations in the GTP cyclohydrolase 1 gene (GTPCH1)\(^{21,22}\). The product of this gene catalyses a rate-limiting step in the production of tetrahydrobiopterin, which itself is an essential cofactor in the conversion of tyrosine to dopamine. It is also a cofactor in the synthesis of serotonin and the metabolism of phenylanaline.

Patients with DRD commonly present in childhood with limb dystonia which gradually progresses. There may be additional parkinsonism, and even mild spasticity and other pyramidal signs. Many patients will show diurnal fluctuation where symptoms are better in the morning and become worse as the day goes on\(^{21}\). There have been many other patients reported with atypical presentations e.g. writer’s cramp, rest tremor and bradykinesia, with some of these patients presenting in their 20’s\(^{23}\). All patients show a dramatic and sustained response to levodopa, without the development of dyskinesias and fluctuations seen in Parkinson’s disease\(^{24}\).

DRD is rather complex to diagnose definitively as the GTPCH1 gene is large, and a huge number of mutations have been reported. This makes gene testing difficult and it is often not readily available. As tetrahydrobiopterin is also needed for the breakdown of phenylalanine, a phenylalanine loading test, where patients are given a drink containing a certain amount of phenylalanine and their plasma levels are measured for some hours afterwards, can be helpful as a diagnostic aid, and will show reduced clearance of the phenylalanine in patients with DRD\(^{25}\). This test is not fool-proof however and false positive and false negative results do occur. In specialist centres it may be possible to measure CSF pterins (such as tetrahydrobiopterin) and this is a more reliable test, and also enables one to look for other deficits in the dopamine synthesis pathway that can rarely cause DRD (e.g. sepiapterin reductase deficiency\(^{26}\), tyrosine hydroxylase deficiency\(^{27}\)).

A trial of levodopa is a pragmatic diagnostic tool, as patients with DRD due to GTPCH1 mutations will all respond well. However, one must be cautious that patients with young-onset Parkinson’s disease, particularly due to Parkin mutations, can present with dystonia and parkinsonism, and would also have an initial excellent response to levodopa. As one would not want to treat such patients with levodopa initially, a DAT scan can be a helpful tool. This will be abnormal in young-onset Parkinson’s disease and normal in DRD. As DRD is treatable, and the clinical picture can be so variable, all patients with young-onset dystonia (< age 30) in whom no clear cause for the dystonia has been identified should have a trial of levodopa.

Myoclonus dystonia

This is an autosomal dominant syndrome characterised by the childhood onset of myoclonus and dystonia\(^{28,29}\). The myoclonus is usually the dominant clinical feature, and the dystonia may be very minimal (when dystonia is absent, such patients are often categorised as “essential myoclonus”). The myoclonus and dystonia typically mainly affect the face, neck and arms, although leg involvement also occurs. The myoclonic jerks are typically very brief – sometimes called “tic-tac” or “lightning” jerks\(^{28,29}\). Both the dystonia and myoclonus usually respond very well to alcohol.

In many patients, mutations are found in the epsilon sarcoglycan gene\(^{30-32}\). This gene is inherited in an autosomal dominant fashion, but shows maternal imprinting\(^{33,34}\). This means that children inheriting the mutation from their mothers will almost never have symptoms, while those inheriting the gene from their fathers almost always will\(^{33,34}\).

Rapid-onset dystonia parkinsonism

This very rare condition causes the rapid onset of generalised dystonia with or without parkinsonism\(^{35}\). The symptoms usually plateau after the period of rapid
evolution, but do not usually recover. The symptoms often seem to be triggered by an infection or other illness. The condition is inherited in an autosomal dominant fashion, and mutations in the ATP1A3 gene have been found in some families.

SECONDARY DYSTONIA

Dystonia may occur secondary to brain lesions, most of which are located in the putamen. Dystonia may develop some months, even years, following the lesion. The dystonia in such cases tends to be hemi-dystonia, and therefore any patient with hemidystonia, even if this is the only clinical finding, should have brain imaging.

Dystonia, in the form of an acute dystonic reaction, can occur secondary to a large variety of drugs. This typically occurs within the first 48 hours of exposure to the drug, and is characterised by dystonic spasm affecting the face and larynx, oculogyric crisis, and often extreme psychological distress. Patients should be managed as a medical emergency, as respiratory problems from bulbar dystonia can result. As well as basic supportive treatment, the offending drug should be withdrawn, and patients should be given anticholinergic medication intravenously to try to reverse the dystonia.

Dopamine receptor blocking drugs, which are a common cause of acute dystonic reactions, also cause movement disorders in a small proportion of patients chronically exposed to these drugs. These movement disorders may consist of choreiform movements, typically of the face (tardive dyskinesia), or tardive dystonia. The dystonia characteristically involves the axial muscles, so patients walk with their back and neck arched. Both syndromes are very difficult to treat. If possible, the offending drug should be withdrawn immediately. If it is not possible to stop the drug, then it should be changed to an atypical dopamine receptor blocker – clozapine has the best evidence for effect, but requires blood monitoring. Other drugs that may help include anticholinergics and baclofen, and deep brain stimulation may also be an option for some severely affected patients.

Dystonia may also occur secondary to infections for example as part of Sydenham’s chorea, and following Japanese B encephalitis.

HEREDO-DEGENERATIVE DYSTONIA

A huge number of degenerative neurological conditions cause dystonia as part of a wider phenotype of neurological dysfunction. Many of these conditions are rare and testing for all of them can be laborious, expensive and sometimes invasive. In view of this a rational approach is needed for patients in whom an heredo-degenerative dystonia is suspected.

The key here is to look for “syndromic associations”. These are symptoms or signs present in the patients in addition to the dystonia which help to greatly narrow down the diagnostic possibilities. For example, if your patient with a suspected degenerative dystonia also has a peripheral neuropathy, then this narrows down the diagnostic possibilities to just a few (e.g. neuroacanthocytosis, spinocerebellar ataxia, metachromatic leucodystrophy).

Table 3 give a list of conditions that cause dystonia as part of a degenerative nervous system disorder. These conditions are divided by their common syndromic associations. Table 4 lists useful diagnostic tests that can be applied after a list of differential diagnosis has been made.

TREATMENT

Treatment of dystonia very much depends on the underlying cause, and the distribution of the dystonia itself. Botulinum toxin injections are the first line treatment for dystonia affecting the face and neck. They have less usefulness in hand dystonia, where hand weakness can occur and may cancel out any improvement in the posture. Patients with generalised dystonia are not generally suitable for botulinum toxin injections, unless they are being used to treat a particular focal problem (e.g. foot posturing that is severely impairing gait).

Medical treatment relies mainly on anticholinergics. These are drugs that have significant side effects, particularly for older patients, but younger patients may be able to build up slowly to large doses with a good effect.
Table 3. Causes of heredodegenerative dystonia classified by their syndromic associations. Adapted from3).

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
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<tbody>
<tr>
<td>Dystonia and parkinsonism</td>
<td>Parkinson’s disease, Progressive supranuclear palsy, Multiple system atrophy, Corticobasal degeneration, Wilson’s disease, Huntington’s disease, Spinocerebellar ataxia (esp. SCA3), GM1 gangliosidosis, Neuronal brain iron accumulation syndrome, Rapid onset dystonia-parkinsonism, X-Linked dystonia parkinsonism</td>
</tr>
<tr>
<td>Dystonia and eye movement disorder</td>
<td>Niemann-Pick C, Ataxia telangiectasia, Spinocerebellar ataxia, Wilson’s disease, Huntington’s disease, Progressive supranuclear palsy</td>
</tr>
<tr>
<td>Dystonia with prominent bulbar involvement</td>
<td>Neuronal brain iron accumulation syndrome, Neuroacanthocytosis, Wilson’s disease</td>
</tr>
<tr>
<td>Dystonia with Ataxia</td>
<td>Spinocerebellar ataxia, Wilson’s disease, Huntington’s disease, DRPLA, Multiple system atrophy, Neuroacanthocytosis, Cervical dystonia and ataxia, GM2 gangliosidosis</td>
</tr>
<tr>
<td>Dystonia with Peripheral Neuropathy</td>
<td>Metachromatic leucodystrophy, Spinocerebellar ataxia, Neuroacanthocytosis, GM2 gangliosidosis</td>
</tr>
<tr>
<td>Other</td>
<td>Mohr-Tranebjaerg syndrome (dystonia and deafness), Aminoacidaemias (infantile onset neurodevelopmental syndromes)</td>
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on the dystonia. Other drugs which are used (without much empirical evidence) include clonazepam (which can be useful for dystonic tremor), tetrabenazine, baclofen and gabapentin. As mentioned above, all patients with young-onset dystonia (< age 30) who do not have a clear reason for their dystonia deserve a trial of levodopa. Occasionally, patients with dystonia which is not DRD are reported to have a limited response to
Peripheral surgical and brain lesion operations for dystonia have now been largely replaced by deep brain stimulation (DBS) of the internal segment of the globus pallidus. This can be a very successful operation for patients with primary dystonia, and has most evidence to support its use in childhood onset generalised dystonia, such as DYT1 dystonia\textsuperscript{14}. Such patients may get an 80-
90% improvement in symptoms which seems to be sustained over time (14). Some patients with treatment resistant focal dystonia have also had benefit from DBS (49-52) as well as patients with myoclonus dystonia (53). Patients with secondary/degenerative dystonia tend to have less response to DBS (54), although in very selected cases such operations may be appropriate, as the small functional gains can make a significant difference to quality of life.

REFERENCES