11 Dystonia: Clinical Features, Diagnosis and Treatment

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Introduction

The dystonias are an unusual group of movement disorders whose main feature is involuntary muscle contraction or spasm. The term dystonia was originally introduced by Oppenheim in 1911 to describe altering muscle tone and postural abnormalities that are seen in this condition. The concept of dystonia can be confusing as the term has been used to describe as symptom (e.g. a dystonic arm posture), a disease (primary torsion dystonia) or a syndrome. The dystonias represent a relatively common group of movement disorders that encompass a wide range of conditions from those where the only manifestation is dystonic muscle spasms, to those where dystonia is one part of a more severe neurological condition.

Definition and Classification

A recent revision of dystonia classification defined dystonia as: a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.[1] The movements range from slower twisting athetosis to rapid, shock-like jerky movements. Dystonic movements can be aggravated by movement (action dystonia) which can be non-specific or task-specific (e.g. writing). Over time the dystonia can occur with less specific movements and eventually can be present at rest leading to sustained abnormal postures.

Three basic approaches are used to classify dystonia: age of onset, distribution of affected body parts (table 1), and aetiology.[2] This descriptive approach has been updated to include other categories including temporal pattern, variability and associated features.[1]

Age at onset

Dystonia can develop at any age, although those with earlier age of onset are more likely to have a severe course affecting more of the body. Divided into infancy (<2 years), childhood (3-12 years) adolescent (13-20 years), early (21-40) and late (>40 years). A more pragmatic division into early (<26 years) and late (>26 years) onset is often used.

Distribution

This divides patients based on whether dystonia is localised to a single body (focal), has spread to contiguous (segmental) or non-contiguous (multifocal) regions, or whether the legs are affected along with other body regions (generalised). Age of onset and body distribution are related: the earlier the age of onset, the more likely dystonia will be severe, spreading to a generalised distribution. In addition, the body region first affected is also important: onset in the legs is most frequent during childhood, and with increasing age the site of onset ascends to the arms/hands, neck and then cranial muscles. Thus childhood limb onset dystonia usually generalises, writer's cramp occurs with mean onset in the 30's and can spread to become segmental dystonia, cervical dystonia has mean onset in the 40's whilst blepharospasm usually starts in the sixth decade and remains focal. The sex of the patient may also influence its onset.[3]

Temporal Pattern, Variability and associated features

This describes whether the dystonia is static or progressive. Variability relates to whether dystonia is persistent, action-specific, diurnal or paroxysmal. The description should also cover if it is a pure dystonia +/- tremor (isolated dystonia) or if there are additional neurological features (combined dystonia).

Aetiology

The third approach to classification is by aetiology.[4] This has been revised a number of times over the years and confusingly uses both clinical and pathological features as well as referring to the presence or absence of genetic factors. This section outlines the difficulties of currently terminology but in addition refers to an alternative (descriptive) classification. It is recommended now that it is best to describe whether there is associated nervous system pathology, genetic or acquired causes or idiopathic (divided into sporadic and familial).

Table 1 Classification of Dystonia

Distribution	Focal - single body part affected	Neck	Cervical dystonia (spasmodic torticollis)
		Eyelids	Blepharospasm
		Mouth	Oromandibular dystonia
		Larynx	Laryngeal dystonia
		Hand or arm	Writer's cramp and other limb dystonias
	Segmental- two or more contiguous body parts	Cranial	Cranial and/or neck
		Axial	Neck and trunk
		Brachial	One arm and axial; both arms +/- neck +/- trunk
		Crural	One leg and trunk, both legs +/- trunk
	Generalised	Segmental crural and any other segment	
	Multifocal	Two or more non-contiguous parts	
	Hemidystonia	Ipsilateral arm and leg	

Epidemiology

The true population incidence and prevalence of dystonia is unknown. The prevalence figures available are usually based on studies of diagnosed cases only and therefore underestimate the real figure. This is particularly the case with dystonia which can present in a variety of ways, and a significant number of cases of focal dystonia are undiagnosed or even misdiagnosed. An early study in the United States based on case note review estimated prevalence for primary torsin dystonia (PTD) to be 329 per million population.[6] More recent studies of diagnosed cases in Japan and Europe estimate prevalence between 101-150 per million.[7,8] The most reliable estimate is from an ongoing study in the North East of England where ascertainment was more complete, and some previously undiagnosed cases were identified. This has produced a prevalence rate of 485 per million.[9] The prevalence of secondary dystonia is unknown although it is estimated from case series that it may be < 20-25% the rate for Idiopathic dystonia.

The most prevalent form of idiopathic dystonia is focal dystonia, of which cervical dystonia is the commonest with prevalence rates reported between 57 and 290 per million population. Rates for blepharospasm are 17 to 80 per million and 14-61 per million for writer's cramp.

A study in South Tyrol in Austria studied a random sample of the population over the age of 50 years.[10] Primary dystonia was diagnosed in 6 of the 707 individuals studied giving a prevalence of 7320 per million in this age selected population, although 95% confidence intervals were very wide at 3190 to 15, 640 due to the small sample. However, this indicates that in the aging population, dystonia is a relatively common neurological disorder.

Clinical Features

The diagnosis of dystonia is based on clinical findings. Isolated dystonia has no other neurological features apart from dystonia and tremor.[2,4] Features that favour a complicated dystonia are listed in Table 2. Investigations are usually performed to help exclude a secondary cause of dystonia.

Table 2 Clinical features that suggest a underlying nervous system disorder

Abnormal birth/perinatal history
Developmental delay
Atypical site for age at onset (e.g. leg onset in adult, cranial onset in child)
Dystonia at rest (rather than with action) at onset
Seizures
Exposure to drugs e.g. dopamine blockers
Continuous progression of symptoms
Prominent bulbar involvement
Hemidystonia
Additional neurological symptoms - pyramidal, cerebellar, cognitive decline, early onset of speech abnormality, parkinsonism
Other systems involved - e.g. organomegaly

Isolated (Primary) Dystonia

Early onset PTD (Dystonia musculorum deformans, Oppenheim's dystonia)

The commonest cause of early onset PTD is mutation in the DYT1 gene on chromosome 9q34, which is inherited as an autosomal dominant trait with reduced penetrance (30-40%).[11] It typically presents in childhood or adolescence (mean age of onset 12 years) with dystonia causing posturing of a foot, leg or arm. Dystonia is usually first apparent with specific actions (e.g writing or walking) but becomes evident with less specific actions with time and spreads to other body regions. No other neurological abnormalities are present apart from postural arm tremor. Disease severity varies considerably even within the same family and isolated writer's cramp may be the only sign. However, around 60-70% of individuals have progression to generalised or multifocal dystonia involving at least a leg and an arm, and often axial muscles. 10% develop segmental dystonia and only 25% remain focal. The cranial muscles are involved in about 10% of individuals.[12]

Key investigations are to exclude treatable differential diagnoses, such as Wilson's disease and Dopa-responsive dystonia. DYT1 dystonia is diagnosed by molecular genetic testing of the *TOR1A* gene, which reveals a 3 base pair deletion in all affected individuals.[11]

Most forms of early onset PTD are genetic in origin and Table 3 lists the genetic forms that have been identified to date. Most are autosomal dominant, some only reported in single families. The gene causing DYT6 dystonia has been identified as *THAP1,* which encodes thanatos-associated protein and may play a role in transcriptional regulation.[15] Screening in other populations have identified mutations in mainly dominant families with brachial and cervical dystonia, usually with prominent laryngeal involvement.[18] In the last year genes for DYT4, DYT23, 24 and 25 have been identified and phenotypes and genes listed in table 3. The existence of autosomal recessive families (DYT2) is controversial.[13]

Focal PTD

These are by far the commonest forms of dystonia.[6,7] Usually sporadic, they have onset in adult life and remain focal in distribution. Autosomal dominant families have been described and it is believed that a proportion of the apparently sporadic cases may represent manifestation of a dominant gene with very low penetrance (estimated at 12-15%). The individual types are discussed below.

Table 3 Genetic Forms of Primary Dystonia

Type	Clinical features	Frequency	Age of onset	Inheritance/ Locus/gene
DYT1[11,12]	Limb onset, generalises, can present as focal	50% cases early onset in non-Jews, 90% in Ashkenazi Jews	Childhood, most present by 26 years	AD *TOR1A* Protein torsinA
DYT2[13]	Focal and generalised	Spanish gypsy families and single Iranian	Childhood to adult	AR, gene unknown
DYT4[14,56]	Laryngeal and cervical, some generalise	Single Australian family	13-37 years	AD, Beta-tubulin
DYT6[15]	Focal or generalised, cranial, cervical or limb	Two Mennonite Amish families	Mean age of onset 19	AD, *DYT6* chromosome 8p21-q22
DYT7[16]	Focal dystonia, cervical and laryngeal	Single German family	28-70 years	AD, *DYT7* chromosome 18p
DYT13[17]	Cranial or cervical, some generalise	Single Italian family	Childhood to adult	AD, *DYT13* chromosome 1p36
DYT21[55]	Generalized/multifocal dystonia, often starting with blepharospasm	Single Swedish family	Adult onset	AD, *DYT21* Chromosome 2q14-q21
DYT23[57]	Late onset cervical dystonia	Large AD family	Adult onset	AD, *DYT23*, CIZ1
DYT24[58]	Craniocervical dystonia	3 Families	Adult onset	AD, *DYT24*Anoctamin 3
DYT25[59]	Cervical and segmental dystonia	Families	Early Adult	*DYT25*, GNAL

Cervical Dystonia (Spasmodic Torticollis)

Cervical dystonia (CD) is a focal dystonia affecting cervical muscles leading to abnormal postures and movements of the head, neck and shoulders.[19,20] It is the single most common form of dystonia, usually with onset in the fifth decade (mean age of onset 42 years) and affects women more than men (ratio 1.4-1.6:1). The dystonic muscle activity can be tonic, phasic or tremulous leading to symptoms of neck pain, head posturing or repetitive jerking producing tremor of the head. CD symptoms tend to worsen over the first 5 years and then stabilise. Twisting of the head around the horizontal axis (torticollis) is the most common movement, present in 80% of patients caused by overactive contralateral sternomastoid and ipsilateral splenius capitis. Laterocollis is seen in 10-20% and is due to overactivity in ipsilateral splenius, sternomastoid and levator scapulae muscles. Retrocollis (head back) and antecollis (head forward) are less frequent . Many patients, however, present with combinations of torti- and laterocollis. Pain is present in 75% of patients and can cause significant disability.

Many CD patients have sensory tricks (geste antagoniste) that can alleviate symptoms. This can involve touching the back of the head, cheek or temple and leads to reduction in abnormal dystonic muscle spasm. Spontaneous remission of symptoms can occur in < 20% of patients, but unfortunately most of these will subsequently relapse. Focal CD can spread to other body parts, including the face and arm but rarely generalises.

The long term complications of CD include cervical spine degeneration leading to radicular or myopathic symptoms. CD also has a significant impact on quality of life and is associated with a higher incidence of anxiety and depression.[21]

Blepharospasm and other cranial dystonias[22]

Blepharospasm is the second commonest form of dystonia and is caused by dystonic muscle spasms of the orbicularis oculi muscles.[7] As for CD, it is more common in females with ratios of female:male of between 1.8 to 2.5:1. Onset is usually in the sixth or seventh decades and is insidious, often with soreness or dryness of the eyes followed by excessive blinking, especially with bright light or reading. This can worsen over months to years, leading to sustained muscle spasms and eye closure and, when

severe, can render a patient functionally blind for significant periods of time. The spasms are sometimes accompanied by perioral muscle involvement.

Oromandibular dystonia can present with either predominant jaw opening (lateral pterygoids, muscles of the floor of the mouth and infra-hyoid muscles), jaw closing (masseter and medial pterygoids) or mixed type. There can also be involvement of the tongue, facial and pharyngeal muscles. Oromandibular dystonia can be present at rest, but often worsens on eating or talking with dysarthria and dysphagia. It is an extremely visible form of dystonia and can be very distressing and stigmatising to patients. Complications include temporomandibular joint impairment and muscular pain.

Writer's cramp and task specific limb dystonias

Writer's cramp is the most common form of task specific dystonia and, in contrast to cranio-cervical dystonia, is more common in males than females.[3,6,7,8] Onset is usually between 30 and 50 years and often starts with a feeling of tension in fingers and forearm interfering with writing fluency.[23] The pen is held abnormally forcefully due to dystonic contraction of hand and/or forearm muscles. Commonly this involves excessive flexion of the thumb and index finger with pronation of the hand and ulnar deviation of the wrist. Individuals may also experience the thumb or index finger lifting off the pen or isolated extension of fingers. Up to 50% of patients also experience upper limb tremor, either on writing or a postural tremor. Strain and aching, particularly in affected forearm muscles, is common on writing, but pain is an uncommon feature.

Writing difficulty is often intermittent at onset, but usually progresses so that cramping starts soon after starting writing. In a minority of patients dystonia occurs on performing other manual tasks, and this can be a feature that develops with time. Spontaneous remission is rare. Many patients whose writing has become illegible, therefore, learn to write with their non-dominant hand. Unfortunately, in up to 10%, writer's cramp can develop in this hand as well.

Dystonic patterns of involuntary muscle contractions are also seen in the context of other highly learned motor skills. These are most commonly seen in professional musicians, craftsmen and sportsmen whose work involves frequent, repetitive movements or particular muscle groups.[24] They have been reported in < 1% of professional musicians, more frequently males. In pianists, for instance, the 4th and 5th fingers of the right hand are most commonly involved, whilst for guitarists the 3rd finger of the right hand is affected. For wind instrument players the hand supporting the instrument and doing fingering at the same time is most involved. Less commonly, lip or orofacial dystonia can develop.[25] Tremor can accompany task specific dystonias in < 40% of cases. Other manual tasks associated with task specific dystonia include typing, painting, and sports such as golf, tennis and snooker.

Laryngeal dystonia

Laryngeal dystonia is relatively rare and can be divided into those case where the predominant problem is spasm of the adductor muscles and those involving abductor muscles.[26] It can occur in isolation or sometimes as part of a segmental cranio-cervical dystonia. Adductor spasmodic dysphonia is the commonest form and is characterised by intermittent voice stoppages, particularly with vowels. This is caused by hyperadduction of the vocal cords due to involuntary spasm of thyroarytenoid and/or lateral cricoarytenoid muscles. Abductor spasmodic dysphonia occurs in about 15% of patients and presents with breathy breaks in speech, especially with consonants. In some cases this is due to involvement of vocal fold opening muscles such as posterior cricoarytenoid and cricothyroid. Spasmodic dysphonia is task specific and only occurs during speech. Laughter, crying and breathing are unaffected. Voice tremor often occurs with both types of spasmodic dysphonia and is also speech specific.

Other laryngeal disorders which can be confused with laryngeal dystonia can occur in other neurological conditions, but the presence of additional neurological signs should alert the clinician to alternative diagnoses. Examples include vocal fold paralysis in motor neurone disease, airway obstruction in multiple system atrophy, hypophonia in Parkinson's disease and abductor vocal fold paralysis in hereditary motor neuronopathy.

Combined Dystonia (Dystonia-Plus) Syndromes

Dystonia-plus syndromes describe a group of conditions that can be distinguished from PTD based on clinical characteristics found in addition to dystonia, or specific pharmacological responses. They usually have a genetic aetiology, but do not have underlying neurodegeneration. The group comprises three distinct conditions, Dopa-responsive dystonia, myoclonus dystonia syndrome and rapid onset dystonia parkinsonism.[4,5]

Dopa-Responsive Dystonia

Dopa-responsive dystonia (DRD or Segawa's disease) was first described in Japan in 1977. Patients typically present with gait disturbance due to foot dystonia in childhood. The dystonia frequently worsens as the day goes on (diurnal variation) and is relieved by rest or sleep. Progression is variable with some patients developing severe generalised dystonia, whilst others develop features suggestive of lower limb spasticity. Parkinsonian features such as bradykinesia and rigidity can develop in later life in some individuals, but can also be the presenting feature in adult life in a minority of cases. Occasionally DRD can present with adult onset limb dystonia (e.g. writer's cramp), cranial or cervical dystonia, or with signs resembling spastic paraplegia. In most cases DRD is inherited as an autosomal dominant trait with reduced penetrance.[27]

The key feature is that DRD shows a dramatic and sustained response to small doses of L-dopa, often as small as 50-200 mg. Benefit is usually apparent within days to weeks and the motor complications of L-dopa treatment seen with Parkinson's disease rarely develop, even with long term treatment. Anticholinergic drugs also can be beneficial.

The principal differential diagnoses for childhood DRD are of early-onset PTD, spastic paraplegia and cerebral palsy and early-onset parkinsonism, especially when caused by mutations in the gene for parkin.[28] The last group of patients often present with dystonia and show good initial response to L-dopa.[29] However, clues to the diagnosis come from inheritance pattern (usually autosomal recessive for parkin) and the occurrence of motor fluctuations and dyskinesias with L-dopa treatment. PET scanning with markers for presynaptic dopaminergic terminals (18F-dopa) or SPECT can also differentiate between the two conditions.

The gene for dominant DRD has been mapped to chromosome 14 (DYT5) and mutations within the gene for GTP cyclohydrolase 1 identified.[30] Numerous mutations have been identified in all 5 exons making genetic testing laborious. Other extremely rare forms of DRD have been reported including a recessive form with genetic deficiency of tyrosine hydroxylase, and also defects in other enzymes involved in pterin synthesis. The diagnosis can usually be confirmed by an excellent response to L-dopa treatment in doses slowly increasing up to 400 mg a day. Alternatively detecting reduced levels of pterins in the CSF or an abnormal oral phenylalanine loading test can substantiate the diagnosis.[31]

Myoclonus-Dystonia Syndrome

Myoclonus-dystonia syndrome (MDS) is characterised by the presence of dystonia in combination with brief lightning like myoclonic jerks.[32] It is frequently inherited as an autosomal dominant trait, caused by mutations in the gene for ε-sarcoglycan (DYT11), although sporadic cases also occur.[33,34] A further autosomal dominant locus (DYT15) has been mapped to chromosome 18.[35]

MDS usually has onset in childhood or early adolescence, with myoclonic jerks affecting the upper limbs and axial muscles (trunk and neck). The myoclonus can occur on rest and also be precipitated by action. Dystonia occurs in around two thirds of patients, with cervical dystonia and writer's cramps the most common forms. Occasionally dystonia affects the legs. Several reports have identified psychiatric features associated with MDS including obsessive-compulsive disorder, panic attacks and anxiety. Most patients note significant relief of symptoms with alcohol or benzodiazepines, and can have marked rebound of symptoms following administration of these. This can often lead to abuse of these substances.

Rapid Onset Dystonia Parkinsonism (RDP)

This is a rare autosomal dominant movement disorder with reduced penetrance. It is characterised by abrupt or subacute onset of both dystonia and parkinsonism with prominent bulbar involvement.[36] Symptoms develop over hours to days with dystonic posturing of the limbs, bradykinesia, dysarthria and dysphagia, postural instability, followed by little or no progression. Onset is usually in adolescence or young adulthood and the subacute extrapyramidal storm can be preceded stable mild limb dystonia for a number of years. Potential triggers in some families include emotional trauma, extreme heat or physical exertion.

Investigation with MRI, CT and PET imaging of the presynaptic dopamine uptake sites have been normal. In some patients reduced levels of CSF dopamine metabolites have been detected. The current assumption is that RDP is due to neuronal dysfunction rather than neurodegeneration.

The condition is rare and only a small number of families have been described with evidence for autosomal dominant inheritance with reduced penetrance. The gene was mapped to chromosome 19q13.2 (DYT12) and recently mutations in the gene for the Na^+/K^+-ATPase $\alpha 3$ subunit (ATP1A3) have been identified in seven unrelated kindreds with RDP.[37] This finding implicates the Na^+/K^+ pump, which is crucial for maintaining the electrochemical gradient across the cell membrane, in dystonia and parkinsonism. Interestingly, mutations in this gene an cause other overlapping syndromes including alternating hemiplegia of childhood and CAPOS syndrome (cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural deafness). [60]

Recently two consanguineous families with autosomal recessive dystonia-Parkinsonism have been described and the causative gene found to be coding for protein-kinase, interferon-inducible, double stranded-RNA –dependent activator.[38]

Dystonia Secondary to Nervous System Pathology

The term secondary implies that an identifiable cause for the dystonia can be found. Many of these directly involve the basal ganglia and lead to contralateral hemidystonia.[39] Table 2 summarises the most common causes of secondary dystonia. Infarcts, tumours, vascular malformations and traumatic injuries to the basal ganglia are well described causes of dystonia, but dystonia may also more rarely occur after injury to cortical, cerebellar or brainstem structures, spinal cord and even peripheral nerve. Perinatal injury may cause dystonia at the time of brain injury (dystonia or choreoathetoid cerebral palsy), or can lead to delayed onset dystonia which can begin years after the injury and progress. Infectious, post-infectious and inflammatory syndromes associated with dystonia usually present in combination with other movement disorders, such as parkinsonism, chorea, athetosis and tics. Drugs may also cause transient or chronic (tardive) dystonia. Acute dystonic reactions occur shortly after the introduction of a drugs and have been described for a number of drugs including dopamine receptor blocking (DRB) drugs, antidepressants (SSRI, MAOI), calcium antagonists, general anaesthetic agents, anticonvulsants (carbamazepine, phenytoin), levodopa, ranitidine, ecstasy and cocaine. Tardive dystonia is usually seen with use of DRB drugs and is defined as dystonia present for at least one month occurring either during or within three months of discontinuation of a DRB. It most commonly affects the face and neck but can spread and even generalise in some cases. Toxins such as manganese and carbon monoxide that can directly affect the basal ganglia also result in dystonia.

Nervous System Pathology: Genetic degenerative Disorders

Dystonia also occurs in a wide range of heredodegenerative disorders which have progressive neuronal loss with a mixture of neurological symptoms and signs, sometimes with systemic involvement.[39] Table 4 lists the various heredodegenerative disorders which can be divided into those with disorders of metabolism, mitochondrial disease, trinucleotide repeat diseases, parkinsonian disorders, and other degenerative processes without defined causes.

Functional Dystonia

The concept of functional (psychogenic) dystonia is difficult due to the fact that in the first half of the 20th century many cases of organic dystonia were thought to be psychiatric in origin due to the unusual and variable nature of the symptoms. However, psychogenic dystonia exists and is a rare

cause of dystonia, often resulting in profound disability.[40-42] As with organic dystonias, it is difficult to diagnose with certainty, and should only be undertaken by a neurologist with considerable experience with organic dystonias. One reason for this is the absence of a specific diagnostic test for dystonia. The diagnosis is based on the presence of clinical inconsistencies and incongruities with organic dystonia. The pathophysiology is poorly understood. Prompt diagnosis and treatment is necessary, given the poor prognosis of conversion disorders when there has been considerable delay between symptom onset and diagnosis and often involves a combination of psychotherapy, physical therapy and psychopharmacologic therapy.

Table 4 Heredodegenerative Disorders with Dystonia

Metabolic Disorders	Metal and Mineral Metabolism	Wilson's disease, Neurodegeneration with brain iron accumulation type I, Neuroferritinopathy, Idiopathic basal ganglia calcification (Fahr disease)
	Lysosomal Storage Disorders	Niemann-Pick disease type C, GM1 and 2 Gangliosidosis, metachromatic leukodystrophy, Krabbe disease, Pelizaeus-Merzbacher disease, Fucosidosis
	In-born Errors of Metabolism	Lesch-Nyhan Syndrome, Triosephosphate Isomerase deficiency, Glucose Transport defects
	Amino and Organic Acidurias	Glutaric aciduria type 1, Homocystinuria, Propionic acidemia, Methylmalonic aciduria, 4-hydroxybutyric aciduria, 3-methylglutaconic aciduria, 2-oxoglutaric aciduria, Hartnup's disease
Mitochondrial Disorders	Leigh Disease, Leber's Hereditary Optic neuropathy, Mohr-Tranenberg syndrome (dystonia/deafness)	
Trinucleotide Repeat Disorders	Huntington Disease, Spinocerebellar ataxias	
Parkinsonian Disorders	Parkinson's disease (especially familial young onset forms), Progressive Supranuclear Palsy, Multiple System Atrophy, Corticobasal Ganglionic degeneration, X-linked dystonia-parkinsonism (Lubag)	
Others	Ataxia telangiectasia, Chorea-acanthocytosis, Rett Syndrome, Infantile Bilateral Striatal Necrosis, Ataxia with vitamin E deficiency, Progressive pallidal degeneration, Sjogren-Larsson Syndrome, Ataxia-Amyotrophy-Mental Retardation-Dystonia Syndrome	

Investigations

Table 5 list potential investigations. However, the clinical presentation will determine which of these are appropriate.[2] For instance a female aged 60 presenting with blepharospasm alone may need no investigation, whilst a child with dystonia and other neurological features would need extensive tests to identify a potential secondary cause. History of birth injury, family history of other neurological disorders or exposure to dystonia-inducing drugs are important.

Hemidystonia is highly suggestive of a contralateral basal ganglia lesion so MRI is mandatory. If MRI is normal, Wilson's disease should be excluded as it is potentially treatable. Slit lamp examination, serum caeruloplasmin and 24 hour urinary copper excretion are required.

Thereafter investigations for metabolic and heredodegenerative disorders will be required with serum amino and organic acids and white cell or fibroblast cultures.

Table 5 Investigation of Dystonia

Dystonia phenotype	Investigation
Isolated torsion dystonia	
Early onset (<26 years)	Copper studies, slit lamp examination
	MRI Brain
	Genetic analysis
	Trial of levodopa
Late onset (> 26 years)	Copper studies, slit lamp if under 50 years of age
	MRI brain
	MRI spine if dystonia fixed or painful
	EMG if painful axial muscle spasm
Combined dystonia	MRI brain/spine
	Nerve conduction studies
	Copper studies, slit lamp, ATP7B gene analysis
	Genetic test for neurodegenerative disorders e.g. Huntington's disease, NBAI etc
	White cell enzymes
	Plasma Biotinidase
	Alpha fetoprotein, immunoglobulins
	Lactate, pyruvate, mtDNA analysis, muscle biopsy
	Blood film for acanthocytes
	Urine amino acids, organic acids, oligosaccharides
	Bone marrow biopsy
	Phenylalanine loading test, CSF pterins
	ERG, retinal examination

Treatment

Treatment options for dystonia have increased dramatically over the last two decades[43]. This has been the result of the use of botulinum toxin and a renewed interest in functional neurosurgery for dystonia. Drugs treatment has some use, particularly for DRD and MDS and the more severe childhood onset primary dystonias. Table 6 lists the treatment options for various forms of dystonia.

Drug Therapy

Drug treatment of dystonia has changes little in the last 20 years. Whilst many forms of dystonia are relatively unresponsive to drugs, there is still an important role for drug therapy for primary generalised dystonia, dystonia-plus conditions and some forms of secondary dystonia.

Dopaminergic Agents

Patients with DRD show dramatic response to low doses of levodopa (with decarboxylase inhibitor) and all cases of young onset dystonia should have a levodopa trial.[44] The mean daily does effective in DRD is 250mg L-dopa, although sometimes higher doses are required. Symptoms of DRD may also respond to dopamine agonists and anticholinergic drugs.

The role of dopaminergic agents in primary dystonia is less clear. Review of small treatment trials suggest that improvement with these drugs was rarely dramatic.[45] 20% felt that they actually deteriorated, but occasionally there was benefit.

Anticholinergic Drugs

Trihexyphenidyl can be useful for childhood onset primary dystonia. One prospective placebo controlled trial found that 67% of patients treated improved and 68% continued to benefit after 2.4 years at a mean daily dose of 40mg. It appears to be less useful in adult onset primary focal dystonia. In both children and adults the dose of anticholinergic must be titrated up gradually to minimise side-effects, particularly of dry mouth, gastrointestinal upset and confusion.[46]

Baclofen

Baclofen is a derivative of GABA that reduces spinal cord interneuron and motor neuron excitability. A retrospective study found it to have useful benefit especially in childhood onset primary dystonia, but only in a minority of adult cases. It appeared to be better tolerated in the younger patients, but significant side-effects of lethargy, dizziness and confusion have been reported.[47]

Intrathecal baclofen (ITB) has been used with benefit, particularly for secondary generalised dystonia, or those with dystonia and spasticity. ITB is administered through an implanted infusion pump connected to an intrathecal catheter which is inserted at around L2-3 level and advanced to C7-T1.

Benzodiazepines

Benzodiazepines have been frequently used, although there is no data from controlled trials. They appear to be effective although use is limited by sedation, ataxia and habituation. Diazepam and clonazepam are most frequently used.

Other Drugs

Numerous other drugs have been used to treat various forms of dystonia. Paradoxically some patients with dystonia appear to improve with use of anti-dopaminergic drugs, such as tetrabenazine and haloperidol. The concern when using dopamine blocking drugs is the development of tardive dystonia and dyskinesia. Other dugs that have been used to treat dystonia in single cases include carbamazepine, propranolol, phenytoin, clonidine, tizanidine, lithium and cannabidiol.

Table 6 Treatment Options for Dystonia

Therapy	Specific	Uses
Drugs	Dopaminergic agents	DRD, sometimes primary and secondary dystonia
	Anticholinergics	Primary and secondary dystonia and DRD
	Baclofen (oral or intrathecal)	Childhood primary dystonia
	Benzodiazepines	Primary and secondary dystonia, MDS
	Antidopaminergic agents	Occasional primary/secondary dystonia
Botulinum toxin	Type A and B	Main treatment of focal and segmental dystonia
Destructive neurosurgery	Selective peripheral denervation	Cervical dystonia
	Myectomy/myotomy	Cervical dystonia/ blepahrospasm
	Intradural rhizotomy/nerve sectioning	Cervical dystonia – rarely used
Functional stereotactic neurosurgery	Pallidotomy, thalamotomy	Primary and secondary generalised or hemidystonia
	GPi Deep Brain stimulation	Primary generalised and segmental dystonia

Botulinum Toxin (BTX)

Botulinum toxin injections are the first line of treatment for focal and segmental dystonias.[43,48,49] BTX consists of a number of serotypes of a potent neurotoxin that acts by inhibiting neurotransmitter release at the neuromuscular junction leading to temporary weakness of the muscle. BTX type A and B are most commonly used in clinical practice. Its principal mode of action in dystonia is to cause denervation of motor endplates, although more recent evidence suggests its effect on sensory symptoms may also be important, possibly by modulating muscle spindle input to the CNS. Local injection of BTX A into overactive dystonic muscles can provide very effective relief of symptoms. Double blind placebo controlled trials have shown BTX A to be efficacious in treating cervical dystonia and blepharospasm (60-70% patients improved), and retrospective and open label studies have also demonstrated its use for laryngeal dystonia, writer's cramp and limb dystonias and selected cases of oromandibular dystonia. BTX has a temporary effect patients require repeat injections at intervals, usually every 12-16 weeks. For uncomplicated cases of blepharospasm and cervical dystonia, muscles to be injected are usually selected clinically. For more complex cases and other types of dystonia, EMG guidance is often required.

The most common side-effects are of unwanted weakness which relates to the dose used and local spread of toxin. Thus for CD, transient dysphagia can be seen, especially when the sternomastoid muscles have been injected. Ptosis is a common complication of injections for blepharospasm. Another problem is the development of resistance to BTX due to the formation of neutralising antibodies, which occurs in up to 10% of patients. The development of neutralising antibodies is a serious problem as it essentially prevents further response to that type of toxin, although the patient may respond to a different serotype of BTX. A new BTX type A free of complexing proteins may reduce the incidence of antibody formation, but this has yet to be shown clinically.[50]

Surgery

Surgical treatment options for patients with medically refractory dystonia have gained increasing acceptance in recent years.[51]

Peripheral Surgery

Peripheral surgery for cervical dystonia and blepahrospasm has been used for those patients not responding to botulinum toxin injections and involves either destruction of nerves supplying the dystonic muscles or myotomy/myectomy, or sometimes a combination of procedures. One of the commonest procedures, selective peripheral denervation, involves sectioning of the peripheral branch of the spinal accessory nerve to the sternocleidomastoid muscle combined with posterior ramisectomy from C1 to C6.[52] Beneficial results have been reported in 70-90% of patients, although there is risk of recurrence and in a retrospective long term study at a mean of 5 years after surgery, there was a reduction in dystonia by 30% in about one third of patients.

For blepharospasm the most frequently used operations are limited or full myectomies of the orbicularis muscles and sometimes corrugator superficialis.

Functional Stereotactic Surgery

Current functional stereotactic options include lesioning and deep brain stimulation (DBS) of the globus pallidus internus (GPi) and the thalamus. Due to the relatively small numbers of patient series, variations in surgical technique, and inconsistent use of outcome measures, no definite recommendations about ideal surgical targets or optimal methods can be made. In general, however, the GPi appears to be the preferred target for primary dystonias. The pallidal target is located in the posteroventral lateral GPi, which is the same site as is used for Parkinson's disease. Pallidotomy has been reported to be effective in various forms of dystonia including primary generalised and segmental dystonia and hemidystonia, with a number of studies reporting 50-80% improvement. In general patients with primary dystonia (especially DYT1) had a better response than secondary cases.[5]

The focus of stereotactic surgery for dystonia is now on DBS because there is a lower risk for bilateral surgery than lesioning. Pallidal DBS is the most frequent stereotactic procedure for dystonia and involves implanting quadripolar electrodes within the GPi and applying continuous stimulation. Unlike DBS in Parkinson's disease, with dystonia it may take months before full benefit of pallidal DBS is seen. However, the dystonia may recur within hours of switching off the implantable pulse generators. DBS has advantages over lesioning surgery as it is reversible and adaptable, avoids the concerns over the effects of lesioning the developing brain in childhood and has lower morbidity for bilateral surgery. However, DBS has problems with hardware and battery failure, high costs and time-consuming follow-up and peri-operative risks of infection and possible hemorrhage.

The most striking results for DBS are found for children with primary (notably DYT1) dystonia. A recent case series found that there was a mean improvement in the Burke-Fahn Marsden motor score of 71% in 15 patients with DYT1 generalised dystonia one year after pallidal DBS.[53] Other case series have found lesser or no effect and it has become clear that case selection is critical, with secondary cases usually showing much less response. There is also some evidence for improvement of primary segmental and focal dystonias, particularly for medically refractory CD.[54] DBS is also used with success for more complex dystonias including myoclonus dystonia syndrome, X-linked dystonia parkinsonism and other secondary dystonias, including tardive dystonia.

Dystonic Crisis (Status Dystonicus)

A rare, but potentially fatal, development is the dystonic storm or crisis. This usually occurs in patients with more severe generalised forms of dystonia, often secondary, where they develop increasingly frequent and relentless episodes of devastating generalised dystonia that can lead to respiratory compromise requiring ventilation. It can be precipitated by infection or drugs changes or even failure of deep brain stimulation (e.g. battery failure). Treatment is difficult but involves combination of drugs including benzodiazepines, anticholinergic drugs and sometimes anti-dopaminergic drugs. Pallidotomy and DBS with pallidal stimulation have become the most successful therapeutic option for this condition. [61]

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