Dystonia

Amit Batla[1]

[1] Amit Batla- MBBS, MD, DM (Neurology). Consultant Neurologist, Luton and Dunstable University Hospital, Luton and Senior Clinical Teaching Fellow, UCL Institute of Neurology, Queen Square, London.

Type of manuscript -Review

The total number of pages: 23

Word count: 4994

Total number of tables: 2

Total number of photographs/figures: 0

Conflicts of interest: None

Address for correspondence

Dr Amit Batla

UCL Institute of neurology,

7, Queen Square, London WC1N 3BG

Email: a.batla@ucl.ac.uk

Introduction

Dystonia is commonly recognized as abnormal postures of a part or whole of the body. Among the movement disorders that are classified based on paucity of movements (hypokinetic) or excess of movements(hyperkinetic), dystonia is a hyperkinetic movement disorder[1]. Clinically the involuntary movements in dystonia are sustained or intermittent muscle contractions that cause abnormal repetitive movements, abnormal postures, or both. With recent advances in the understanding of dystonia, tremor is increasingly being recognized as one of the presentations of abnormal repetitive movements that results from underlying dystonia[2]. These movements are usually patterned and based on body distribution these may be seen in a single body part (focal), two or more contiguous body parts (segmental), or two or more non-contiguous body parts (multifocal). Depending on the spread of these movements, hemi-dystonia (one side) and generalized dystonia (>2 contiguous body parts plus trunk) can be seen. The commonest clinical presentations of dystonia in adults are cervical dystonia (cervical torticollis), focal hand dystonia (writer's cramp) and in children, generalized dystonia (oppenheim's or torsion dystonia) are commoner. Wilson's disease and inherited metabolic disorders including dopamine responsive dystonia are common in clinical practice of movement disorders in India. Because of the multiple underlying aetiologies of dystonia and a variety of clinical features, it is recommended now to use a classification of dystonia using two axes. Axis one is for clinical features and phenomenology and axis two is for aetiology. This classification system acknowledges the significant overlap that might be seen in presentation of dystonia due to various underlying pathologies (Table 1). This article provides a contemporary review of the clinical approach, aetiological considerations and management options available for dystonia.

Phenomenological considerations that help recognise dystonia

Dystonic movements are caused by co-contraction of agonist and antagonist muscles that can manifest as

- Abnormal postures that are typically mobile (not fixed) with or without twisting movements
- Slow writhing movements (athetosis)
- Dystonic tremor

Although dystonia can involve several body parts and muscles, the nature of the abnormal postures is ‘repetitive’ or ‘patterned’. This implies that it consistently involves the same muscle groups. This consistency and pattern helps distinguish dystonia from other hyperkinetic movement disorders such as chorea which are non-patterned and much more variable. When differentiating dystonia from other hyperkinetic movement disorders, it is worth noting that dystonic movements cannot be suppressed like tics or have the urge associated with them. Although hyperkinetic by definition, dystonia is much slower than chorea and myoclonus. Athetoid movements can occur, where the dominant muscle activity switches from agonist to antagonist and vice versa.

The differentiation of dystonic tremor from essential or other varieties of tremor is much less concrete in clinical practice and it may be difficult to have a consensus even among movement disorders specialists on this matter[2]. By definition, dystonic tremor is jerky, irregular and variable in amplitude, and typically worsens in particular positions of the affected body part. Tremor occurs commonly with dystonia. If the tremor affects the body part where dystonia is present it is called a dystonic tremor. If tremor is seen in another body part not directly affected by dystonia, it is rather termed tremor associated with dystonia.

A clinical examination clue to help identify dystonia is that dystonia is often aggravated by voluntary movement. Action dystonia is characterized by dystonic movements only with action or voluntary movement. When dystonia is manifested only with specific tasks, it is called task-specific dystonia; such as writer's cramp and musician's dystonia (embouchure). Other factors that tend to exacerbate dystonia include fatigue and emotional stress, whereas the movements usually decrease with relaxation or sleep.

Another characteristic of dystonic movements is 'overflow'. This is defined as activation of dystonic movements by actions in parts of the body remote to the affected area. Examples include leg dystonia while writing or axial dystonia with talking.

Dystonia can often improve by tactile or proprioceptive sensory tricks (*geste antagoniste*). Often a patient will be able to improve to some degree the abnormal posture by touching, or even sometimes thinking about touching the affected body part. [3,4]. Sensory involvement in dystonia is quite unique compared to other movement disorders. Though tics have a sensory phenomenon of 'urge' this is quite different. An 'urge' precedes and initiates a movement (tic), though *geste* is used to stop an involuntary movement or correct an abnormal posture in dystonia.

Despite the 'motor' definition of dystonia, it is increasingly being recognized that non-motor features are seen in many patients with primary dystonia, [5,6]. These include disease-related pain, mild sensory symptoms, and depressive disorders [7-10] These non-motor symptoms are clinically relevant, and must be recognized early as they can impair quality of life almost as much if not more than the motor symptoms. [11-13].

An approach to dystonia classification

The classification scheme of dystonia has changed several times in the last 20 years. The changes or advances in classification are useful for clinical practice and helps accurate

diagnosis and thereby has a significant bearing on management and medical research. Some approaches to classification are discussed here briefly and evolution of terminology is summarized in table 1.

1. Dystonia can be young-onset (< 20-30 years, 25 years is a rough guideline) and late-onset dystonia (after 26 years). The new scheme of classification uses axis 1 for defining age of onset.

2. Dystonia has been classified based on the aetiology in to primary, secondary, heredo-degenerative dystonia and dystonia plus syndromes. In the new consensus (2013)[1] this has been taken out (table 1) and replaced with axis 2 (aetiology).

3. Dystonia can be classified by distribution as focal, segmental, multifocal, hemi-dystonia and generalized dystonia. This is retained in current classification and is very useful form management perspective[1,14].

a) *Focal dystonia*: The abnormal movements involve a single body part only, and includes
    i. Writing dystonia (Writer's cramp) (hand/finger hyperextension, flexion or other abnormal posturing of writing apparatus only while writing).
    ii. Cervical dystonia (spasmodic torticollis): Rotation, lateral bending, lateral tilting, flexion or extension abnormality of neck.
    iii. Blepharospasm is bilateral eye closure produced by spasmodic contractions of the orbicularis oculi muscles.
    iv. Oromandibular dystonia, jaw or mouth closure with trismus and bruxism, or involuntary jaw opening or deviation.
    v. Lingual dystonia, laryngeal dystonia (spasmodic dysphonia) and geniospasm are other forms of focal dystonia.

vi. Others such as hemimasticatory spasm are rare forms of dystonia. Although commonly seen in botulinum toxin injection clinics, it is worth emphasizing here that hemifacial spasm or synkinesis is not a form a dystonia but a cranial nerve disorder.

b) *Segmental dystonia*: The abnormal movements affect two or more contiguous body parts (eg. arm and neck)
   i. Craniocervical dystonia is characterized by a combination of blepharospasm, oromandibular, lingual, facial, laryngeal, and cervical dystonia.
   ii. Brachial (one or both arms with or without the involvement of neck or cranial muscles)
   iii. Crural (one leg plus trunk or both legs)
   iv. Axial (neck and trunk with or without cranial muscles).
c) *Multifocal Dystonia*: two or more noncontiguous body areas are involved (eg right arm, left leg).
d) *Hemidystonia*: affects one side of the body
e) *Generalized Dystonia*: involves two or more contiguous body parts in addition to the trunk.

A clinical approach to dystonia

It is recommended to use the two axes to approach dystonia and investigate the aetiology[14]. As elaborated in table 2. Some specific dystonia syndromes and their clinical features are further elaborated below.

Childhood onset isolated dystonia

The commonest genetic cause of young onset primary dystonia is *DYT1* dystonia (Oppenheim dystonia, dystonia musculorum deformans). It is characterized by early onset

(mean age 13 years), affecting a limb initially (leg or arm is affected first in 90% of cases) and progresses to generalized/multifocal (65%) involvement while spread to cranial structures is less common (15-20%).[15,16] However, there is a wide phenotypical and intrafamilial variability, from severe dystonic storm to mild writer's cramp as well as various atypical phenotypes. [17,18] . *DYT-6* dystonia is a common cause of generalized dystonia but commonly starts with focal, (laryngeal or craniocervical) involvement.

Combined dystonia in childhood to adulthood without nervous system pathology

Dystonia myoclonus

The *DYT11* myoclonus-dystonia (MD) is characterized typically by myoclonic jerks and dystonia that usually begins very early in childhood. Myoclonus is the commonest presenting symptom and most often affects the neck, trunk, and upper limbs. Unlike myoclonic epilepsies, legs are less prominently affected. The myoclonic jerks typically show a dramatic response to alcohol [19,20]. The jerks are not stimulus-sensitive indicating a subcortical origin. About two thirds of patients with *DYT11* show dystonia, mostly cervical or writer's cramp, which tends to remain mild. Psychiatric manifestations including, depression, anxiety, panic attacks and obsessive-compulsive disorder (OCD) have been reported and in particular, OCD has been found in those not affected with motor signs suggesting it is related to the genetic defect. [21-23]

Dystonia-parkinsonism

DYT3 is the only form of dystonia that is inherited as an X-linked trait. Onset occurs in the mid-thirties (range 12-52 years) with complete penetrance by the end of the 5th decade. The symptoms start as focal dystonia in almost any part of the body and progress to multifocal or generalized dystonia in most cases within 5 years. Parkinsonism evolves later in the disease in about 50% of the patients [24,25].

DYT5a was initially described by Segawa in 1976 [26] and later by Nygaard and colleagues as dopa-responsive dystonia (DRD) because of the dramatic and sustained response to low dose of levodopa [27]. The typical phenotype includes childhood (average 6 years) limb onset dystonia with diurnal variation (e.g. worsening of the symptoms as the day progresses), improvement after sleep and dramatic response to levodopa. With the identification of the disease gene, the clinical spectrum of DRD has expanded to include oromandibular dystonia, spasticity with developmental delay mimicking cerebral palsy, psychiatric abnormalities and generalized hypotonia with proximal weakness.[28,29]

In a minority of cases DRD can also be inherited as an autosomal recessive disorder with mutations in the genes coding for other enzymes involved in dopamine synthesis including tyrosine hydroxylase (TH) (often referred to as *DYT5b*) [29,30], sepiapterin reductase (SR) and aromatic L-amino acid decarboxylase (AADC) deficiency [31]. The clinical manifestations are often more severe and less responsive to dopamine. The spectrum can include mental retardation, oculogyric crisis, ptosis, hypotonia, severe bradykinesia, drooling and seizures. Presence of these features in patients with early onset dystonia responsive to dopamine must prompt cerebrospinal fluid (CSF) analysis for pterins and products of dopamine pathway.

A further dystonia-parkinsonism syndrome has been designated the *DYT12* locus, which was mapped to chromosome 19q13. [32,33] The disease phenotype designated rapid onset dystonia-parkinsonism because of key clinical features including abrupt onset, within hours to weeks, of dystonia with signs of parkinsonism usually triggered by physical or emotional stress (fever, child birth, running, alcohol binges). The age of onset varies from 4 to 58 years but typically presents in the teens or early twenties and the distribution follows a rostro-caudal (face>arm>leg) gradient with prominent bulbar involvement.

An autosomal recessive form of dystonia-parkinsonism, *DYT16*, was assigned to chromosome 2q31 [34]. The phenotype in these patients is characterized by early (2-18 years), limb onset with progression to generalized dystonia including prominent bulbar involvement with spasmodic dysphonia, dysarthria, and even dysphagia. Some affected members also had parkinsonism.

It is recommended that in absence of obvious contraindications, all cases of young onset generalized dystonia must be tried on Levodopa to exclude Dopa responsive dystonia (DRD) due to GTP cyclohydroxylase-1 (GCH-1) deficiency. Also called Segawa syndrome, DRD is commoner in females and is associated with worsening of walking diurnally. The other forms of DRD can be due to defects in dopamine synthesis pathway and can manifest with episodes of oculogyric crisis, skeletal abnormalities, and seizures. Perinatal hypoxic injury leads often to severe generalized dystonia with or without spasticity and this is often called athetoid cerebral palsy and should be differentiated from DRDs.

Combined dystonia in childhood to adulthood with nervous system pathology

Although dystonia is typically not progressive if it follows a static brain pathology such as perinatal infract or brain lesion, there could be an initial worsening of the symptoms after the event for up to some years and then the condition becomes static. Continuous progression should raise suspicion for degenerative causes of dystonia. [35,36] Past medical history, abnormalities in the neurologic examination, neuroimaging, or laboratory evaluation; distribution (e.g. hemidystonia); age at onset and distribution, which is unusual for primary dystonia such as young-onset cranial dystonia or late-onset lower limb dystonia, are clues for the diagnosis of secondary dystonia.

Brain injury or infection (e.g., perinatal injury, stroke, head trauma or peripheral trauma, brain tumor, exposure to neurotoxic agents, Japanese B encephalitis, encephalitis lethargica,

brain abscesses) especially involving the basal ganglia (mostly putamen), cerebellum, and thalamus[37]Perinatal hypoxic injury leads often to severe generalized dystonia with or without spasticity are commonly associated with combined dystonia and this is often called athetoid cerebral palsy and should be differentiated from DRDs.[29,38,39]

Dystonia due to degenerative nervous system pathology

Inherited degenerative diseases that can cause dystonia include many autosomal-dominant and autosomal-recessive conditions, X-linked dominant and recessive conditions, and mitochondrial defects. As per definition there are other symptoms and signs, and dystonia occurs as part of neurodegeneration. The most important conditions, along with the responsible genes are included in table 2.

Wilson's disease is a common cause for dystonia which can be generalized, segmental, or multifocal, but cranial involvement is characteristic; other common signs include "sardonic" smile, wing-beating tremor, dysarthria, dysphagia, drooling, ataxia, and dementia. In addition to brain and liver (cirrhosis, acute hepatitis) involvement, systemic findings can involve the eye (Keyser-Fleischer rings), heart, kidney, bones, joints, glands, and muscles. As this condition is potentially treatable, this condition must be kept in mind when seeing any patient with movement disorders.

Late adult-onset isolated dystonia

Focal dystonia is more common in adults, which can become segmental, with spread of symptoms over some years and then plateau. Lower limb dystonia is very unusual for isolated dystonia at this age and isolated lower limb dystonia after age of 30 should raise the possibility of Parkinson's disease. Traditionally, adult onset primary dystonia are thought to be sporadic, but recently there is evidence that at least the tremulous type of cervical dystonia is more likely to be familial[40].

Cranio-cervical or cervical dystonia is the most common adult onset primary dystonia. Most commonly these are idiopathic, but some genes have been linked to this presentation (Table 2).

Genetic forms of cervical dystonia have been recognized. *DYT13* is an autosomal dominant disorder with adolescence-onset mainly segmental dystonia and prominent cranio-cervical involvement[41] . *DYT17* is a rare form of dystonia with autosomal recessive inheritance and segmental dystonia or generalized dystonia sometimes with severe dysphonia and dysarthria.[42]. *DYT 24* presents with tremulous cervical dystonia due to ANO3 mutations[43]. *DYT 23* linked to *CACNA1B* gene[44] and *DYT25* due to *GNAL* mutations also present with focal onset dystonia[45,46].

Typical age at onset for idiopathic cervical dystonia is around 55 years, and women are more often affected than men. It can start with gradual onset of discomfort or pain in the neck, and often confused with cervical spondylosis or degeneration in earlier stages of the condition. As symptoms progress, involuntary pulling of the head in any direction can be more visible. Various combinations of neck muscles may be involved to produce abnormal head positions, including horizontal turning (torticollis), tilting (laterocollis), flexion (anterocollis), or extension (retrocollis). Jerky tremor, which worsens by turning the head towards the normal position is very common and can be the predominant feature. Patients may have a *geste antagoniste* (more common in primary dystonia), where they can partially relieve their spasm by touching the chin or part of their face. Symptoms usually progress over 6-12 months and then plateau. Remission can occur in 10-15% of the patients, especially those with younger onset and may be sustained.

Idiopathic focal dystonia

Blepharospasm causes contraction of the orbicularis oculi muscles; it tends to start later than other cranio-cervical dystonia, with mean age at onset around 63 years, while women are more commonly affected than men (3:1). An uncomfortable feeling around the eyes, dry eyes, photophobia may precede the spasm. Mild cases are characterized by increased blink rate with flurries of blinking, whereas more severely affected patients have visual impairment due to sustained forceful eye closure. In some patients there is an inability to activate the levator palpebri, so that the eyelid cannot open, and this is called levator inhibition. About two thirds of the patients are significantly disabled and 12-36% of them are considered functionally blind. [47]

Spasmodic dysphonia (SD) results from dystonia of the vocal cords and has a similar age at onset and sex ration to cervical dystonia. Compared to other forms of cranial dystonia, it occurs less often in conjunction with other cranial dystonia. [48] It is estimated that the majority of the patients have isolated SD, about 10-15% progresses to another cranial region, and about 5% to extracranial sites. [49,50] In adductor dysphonia (the most common form), which involves the thyroarytenoid muscles, there is excessive glottal closure in a rigid fashion preventing air flow and causes a strained, strangled voice. If associated with generalized dystonia, *DYT-6* must be considered in differential. Abductor dysphonia (much less common), involves the posterior cricoarytenoid muscles, is characterized by open glottal configuration and a paucity of vocal cord vibration so that the voice sounds whispering and breathy.

In **oromandibular dystonia** (OMD) there is abnormal activity in lower facial, tongue, jaw, and pharyngeal muscles also affecting sometimes the platysma. It has a similar age at onset to cervical dystonia and women are more commonly affected than men. Jaw closing dystonia has been considered to be the most common form, while simultaneous movements of jaw openers (lateral pterygoids, digastric muscles) and closers (medial pterygoids, masseter and

temporalis muscles) may result in jaw tremor [51]. OMD may cause pain and difficulty in speaking, chewing and swallowing. Sensory tricks like putting a finger in the mouth, chewing gum or placing a toothpick in the mouth can partially help reducing the symptoms [52]. An important differential diagnosis is OMD caused by neuroleptic drugs, since this presents with a similar clinical picture. A combination of blepharospasm and OMD is called **Meige's syndrome**.

Primary **lingual dystonia** is rare and may or may not be associated with OMD. Although severe tongue protrusion dystonia is more frequent in combined dystonia[53], it has been described also with antipsychotic drugs. [54] Tongue movements may be repetitive, or protrusion may be sustained. Movements are often action-induced, commonly with speaking[55] and tongue may also curl instead of protruding. [56]

Task specific dystonia

The most common adult onset limb dystonia is writer's cramp, where the patient shows abnormal postures affecting the hand when writing, but not while performing other tasks. Age at onset is around 25-35 years and men are more commonly affected than women. The unaffected hand may show mirror movements when writing with the affected hand. Other adult-onset limb dystonia include task-specific dystonia like musicians, typists, or golfers' dystonia.

Musician's dystonia is a focal task-specific dystonia (FTSD). A genetic contribution has been suggested to musician's dystonia with phenotypic variability. It may encompass embouchure dystonia affecting mouth, finger and hand dystonia in pianists, or organ players.

Paroxysmal dystonia

Paroxysmal dystonia represents conditions where dystonia may occur as paroxysms or episodes. Based on precipitating event, paroxysmal dystonia is subdivided into kinesigenic (PKD), non-kinesigenic (PNKD), and exercise-induced forms (PED).

Paroxysmal non-kinesigenic dyskinesia (PNKD) is characterized by attacks of dystonia, chorea, ballism, or athetosis. These are often provoked by alcohol or caffeine but sometimes no triggers are identified. The episodes last from minutes to hours with a frequency between once per day to one or two per year. The age of onset is typically in childhood or adolescents but can be as late as 50 years [57]. PNKD has one known gene *DYT8* (PNKD1) [58-60] and one locus, *DYT20* (PNKD2) [61].

Paroxysmal kinesigenic dyskinesia (PKD) is characterized by short (seconds to minutes) frequent (up to 100 times per day) attacks of dystonic or choreiform movements precipitated by sudden movements. Age of onset is usually during childhood or adolescence, but symptoms can resolve in adulthood. PKD has one known gene *DYT10* the *PRRT2* (proline-rich transmembrane protein 2)[62,63] and a second locus for PKD has been designated *DYT19* [64]

Paroxysmal exercise-induced dyskinesia (PED) is characterized by exercise induced attacks of dystonic, choreo-athetotic, and ballistic movements, affecting the exercised limbs which last from a few minutes to an hour. The disease usually onsets in childhood and can have other disease manifestations including epilepsy, migraine, developmental delay and hemolytic anemia. It shows an autosomal dominant inheritance pattern with slightly reduced penetrance. *DYT18* is known with mutations in the *SLC2A1* gene encoding glucose transporter 1 (GLUT1)[65].

Drug induced dystonia

Exposure to **dopamine receptors blocking drugs** (DRB) or other agents (amine depletors, serotonin-reuptake inhibitors, monoamine-oxidase inhibitors, calcium antagonists,

benzodiazepines, general anesthetic agents, carbamazepine, phenytoin, triptans, ranitidine, cocaine, ecstasy) is a common cause of secondary dystonia. **Acute dystonic reactions** may occur in up to 2% of patients beginning treatment with DRBs. Time to onset is variable but 50% will develop dystonia within 1-2 days and 90% within 5 days. Common presentations are OMD, oculogyric crisis, cervical dystonia and laryngeal dystonic spasm. **Tardive dystonia** is caused by chronic exposure to DRBs. All neuroleptic drugs including the atypical with the exception of clozapine can cause tardive dystonia.[66] In contrast to acute dystonic reactions, amine depletors (e.g. tetrabenazine) do not cause tardive syndromes. Clinically it ischaracterized by axial dystonia with hyper-extension of the spine and retrocollis. The mean time from exposure to onset is around 6 years but the shortest exposure time to onset reported is 4 days. Around 10% of the patients show spontaneous remission, while the prognosis of the rest depends on the prompt discontinuation of the DRB and the total duration of the exposure. [66]

When it is not dystonia

A variety of central and peripheral nervous systems disorders, as well as non-neurologic conditions, can be associated with abnormal postures that resemble dystonia such as neuromyotonia, myotonic disorders, inflammatory myopathies, and glycogen storage diseases. Stiff-person syndrome causes contraction of axial and proximal limb muscles. Carpopedal spasms of tetany can be the manifestation of hypocalcemia, hypomagnesemia, or alkalosis. Orthopedic and rheumatologic processes involving bones, ligaments, or joints can result in abnormal postures. In Sandifer syndrome, patients (typically young boys) with hiatal hernia develop head tilt in association with gastroesophageal reflux. Psychogenic dystonia can be a part of conversion disorder and is not classified with dystonia syndromes. It is commonly fixed compared to organic dystonia. Fixed dystonia can manifest with skin changes and complex regional pain syndrome. There can be an immediate placebo like

response to botulinum toxin in fixed dystonia.

Investigative approach to dystonia

Basic investigations

Specific blood tests for investigating dystonia include copper, ceruloplasmin, white cell enzymes, acanthocytes, lactate, pyruvate, Creatine Kinase and antinuclear antibody screen to look for systemic disorders causing nervous system pathology. They should be individualized based on clinical picture and associated features as indicated. Specific clinical findings or laboratory abnormalities may dictate further investigations, including electrophysiological studies to assess for associated myopathy, neuropathy as indicated. Lumbar puncture is useful to study dopamine pathway metabolites and can guide further genetic testing if a patient is suspected to *GCH1* negative DRD.

Muscle or skin biopsy, or metabolic studies of blood, urine may be helpful to investigate for rarer causes such as mitochondrial and metabolic disorders, amino acid and lysosomal storage disorders.

Magnetic resonance imaging (MRI) of brain is not always necessary particularly in isolated focal or generalized dystonia. If metabolic disorders involving iron or copper are suspected, MRI with sequences to detect iron may be useful to identify eye of the tiger sign in Pantothenate kinase associated neurodegeneration or cortical pencil lining in neuroferritinopthy[67]. MRI is also useful in other heredodegenrative cases particularly Wilson's disease and may show radiological signs of Wilson's.

Dopamine transporters imaging can help in documenting dopaminergic depletion in parkinsonism when diagnosis is in doubt. One should also keep in mind the possibility of psychogenic dystonia if there is variability and the clinical and investigation profile do not

follow a recognizable pattern. Psychogenic dystonia can be diagnosed based on established clinical criteria.[68]

Genetic testing

It is recommended that *DYT1* testing should be offered for patients with limb onset, primary dystonia with onset before age 30, as well as in those with onset after age 30 if they have an affected relative with early-onset dystonia. Data to guide *DYT6* testing are insufficient at present. Most patients with clinically typical DRD will have identified mutations in *GTPCH1* if comprehensive analysis is performed, including testing for deletions. There is genetic testing for myoclonus-dystonia *DYT11,* although many sporadic cases do not harbor *SGCE* mutations. Evaluation of secondary/heredo-degenerative dystonia is dictated by clues provided by the history and examination.

Approach to Treatment for dystonia

Treatment of dystonia is possible with drugs, botulinum toxin injections and deep brain stimulation surgery.

Treatment with oral medication

Trihexiphenidyl is an anticholinergic drug that is useful in generalized and focal dystonia[69]. The usual starting dose is 1 mg daily and increase by 1mg every 4-7 days to reach 1mg tds. Then increase by 1mg every 4-7 days to reach 2-4 mg tds. In case of side effects dose titration must be stopped and reattempted after 1-2 weeks. The maximum dose is 50-100mg/day. Common side effects are dry mouth, dry eyes, nausea, confusion, memory complaints, hallucination, constipation, and urinary retention. Anticholinergics are contraindicated with closed angle glaucoma, and known urinary retention.

Tetrabenazine is a dopamine-depleting drug, an inhibitor of vesicular monoamine transporter 2. At present there is insufficient evidence to support the use of tetrabenazine for focal dystonia, but it is still commonly used for generalized dystonia. The usual starting dose is 12.5 mg once daily and increase 12.5 mg every week to reach 12.5 mg three times a day. Average dose is 25-50 mg three times a day and maximum dose is 200 mg per day. This drug should be avoided in depression as it is known to increase chances of suicide. Tetrabenazine should not be used in dystonia with parkinsonism.

Clonazepam is a benzodiazepine, which acts as a muscle relaxant and commonly used for its benefit in generalized dystonia. The starting dose is 250μg once daily increased by 250μg every week to reach 500 μg to 1mg bd or tds and maximum dose is 4-6 mg/day. As this can cause sleepiness, machine operation and driving may be at risk and professions involving these activities are relative contraindications.

Treatment with Botulinum toxins[69]

There are 7 serotypes of Botulinum toxins labelled as A-G. The type A and B are available for clinical use in dystonia. Each serotype binds to a serotype-specific acceptor site on presynaptic nerve terminals, and each selectively cleaves a specific protein involved in vesicle fusion and neurotransmitter release. Doses and site of injections vary based on clinical phenotype. Caution is advised when injecting in the presence of pre-existing muscle neuromuscular weakness due to disorders such as amyotrophic lateral sclerosis, myopathies, motor polyneuropathies, and myasthenia gravis or Lambert-Eaton syndrome and concurrent use of aminoglycoside antibiotics or other neuromuscular blocking agent. Patients with known bleeding disorders, or regular use of anticoagulants such as warfarin will need to have international normalized ratio (INR) monitoring before injecting as there is a significant chance of haematoma formation. Patients on newer anticoagulants such as Apixaban will

need to miss a couple of doses around injections, but advice must be taken from haematology regarding this before injecting. Safety and efficacy of Botulinum toxin injections are not established in patients less than 16 years of age for the treatment of cervical dystonia, and in patients less than 12 years of age for the treatment of blepharospasm and strabismus. There is insufficient data to allow use of Botulinum toxin in pregnancy and lactation. Main side effects are excessive weakness of muscles injected, spread to adjacent muscles causing weakness. Other side effects include fatigue, flu-like symptoms, a dry mouth, dizziness and a skin rash, local pain or bruising at injection site is common side effects irrespective of the site of focal dystonia.

Treatment with DBS

DBS is a useful option for the treatment for primary generalized and segmental dystonia[68]. Bilateral globus pallidus interna (GPi) is the preferred site if DBS is considered and the complications rate is similar to DBS procedures done for other conditions. The DBS device consists of three components: a lead with four electrodes (contacts), which is implanted within the deep brain target usually the GPi in this case and a programmable pulse generator, which is used to deliver the therapeutic current. This is usually implanted in the chest wall. After lead implantation, the pulse generator can be programmed transcutaneously from the chest wall. The current accepted target of DBS for dystonia is the globus pallidus internus (GPi). Usually the site of electrode is localized using microelectrode recording, with or without intraoperative MRI guidance. The device is activated 7 to 14 days after implantation. The amplitude, pulse width, frequency, and choice of the active contacts can be regulated. There is no consensus regarding the optimal settings for treatment of dystonia. Wide pulses (210–400 μsec) and high frequencies (130 Hz or higher) are preferred. Using lower settings prolongs battery life, therefore requiring fewer battery replacement surgeries. With availability of batteries with longer lives or options of recharge, this may not be a problem.

The duration of affect varies in different studies. There is an immediate lesioning effect and cervical dystonia improves but returns in a week. The contraindications for DBS include psychiatric disease, cognitive impairment, swallowing difficulty or possible incompliance with the required close follow-up for programming and maintenance of the device after the surgery are contraindications. Psychiatric side effects may limit the success of the surgery. Patients with poor performance in neuropsychological testing, especially in frontal lobe and memory domains, may not be suitable candidates and may be at risk for worsening with DBS. Known complications include intraoperative haemorrhage or ischemia, perioperative infection, displacement or fracture of the extension cable, are uncommon complications[69].

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