

CHAPTER 18

Primary Dystonia

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Definition and classification

The term dystonia was introduced to describe patients with severe generalized abnormal movements and postures, who were believed to have an alteration of muscle tone (hence the word 'dystonia') (1). The phenomenological description coincided with the generalized phenotype for many decades. In June 1975, an international conference chaired by Stanley Fahn in New York recognized the clinical features of focal forms of dystonia (2). Later, David Marsden proposed gathering together under the heading of dystonia nosologic entities that were previously considered independent forms (e.g. blepharospasm, torticollis, 'spastic' dysphonia, writer's cramp) (3–5). Finally, in 1984, an ad hoc committee of the Dystonia Medical Research Foundation documented the occurrence in all forms of dystonia 'of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures' (6). Later, the basic clinical features (dystonic movements and postures) and additional clinical features (activation/deactivation) of dystonia were described (7, 8).

Classification of dystonia syndromes has changed over time. Fahn and Eldridge (2) first distinguished primary dystonia (with or without hereditary pattern), secondary dystonia (with other hereditary neurological syndromes or due to known environmental cause), and psychological forms of dystonia. Later, Fahn, Marsden, and Calne proposed a classification of dystonia based on three axes, describing for each patient the age at disease onset (early vs adult), distribution of involved body sites (from focal to generalized), and aetiology (differentiating idiopathic dystonia syndromes, sporadic or familial, from symptomatic ones) (6, 9). The first two axes have remained unchanged over years, whereas the aetiological classification has been expanded to include four subgroups of dystonia syndromes: primary, dystonia-plus (i.e. dystonia with parkinsonism or myoclonic jerks), secondary, and hereditodegenerative (10).

The recently published European dystonia guidelines (11) refine the aetiological axis distinguishing primary (or idiopathic) syndromes, hereditodegenerative (where dystonia is a feature of a genetic disorder characterized by neurodegeneration) and secondary (or symptomatic) syndromes (Table 18.1). Based on the phenotype, primary dystonias are further subdivided into primary pure (with dystonia only), primary-plus (with other associated movement disorders), and primary paroxysmal (characterized by intermittent symptoms). This classification has recently been revised by

an ad hoc committee which convened in Grottaferrata, Rome, in May 2011 (consensus not yet published).

Phenomenology of primary dystonia

Dystonia can occur at rest, during voluntary movement, or in paroxysmal form, following a specific trigger. These features must be appreciated by expert clinical examination and are best observed in primary dystonia forms. The clinical picture becomes more complex when dystonia features are combined or intermixed with other movement disorders in dystonia-plus syndromes.

Cardinal features

Following Marsden's seminal observation (12), it is commonly accepted that dystonia encompasses a combination of movements and postures to generate sustained muscle contractions, repetitive twisting movements, and abnormal postures (torsion dystonia). Dystonic postures can precede the occurrence of dystonic movements, and in rare cases can persist without appearance of the latter (fixed dystonia) (7). Dystonic movements have specific features that can be recognized by clinical examination: speed of contractions may be slow or rapid, but at the peak of movement it is sustained; movements almost always have a consistent directional or posture-assuming character. Dystonic movements and postures are commonly aggravated during voluntary motion, and in milder forms they may only occur during some specific voluntary actions (task-specific dystonia).

Dystonic movements may be regular, appearing as tremor (dystonic tremor (13)). When they are fast and jerky, they may resemble myoclonus. Dystonic tremor may precede clear abnormal posturing, and its occurrence in isolation may lead to the diagnosis of dystonia being missed (7). A tremor similar to essential tremor may occur in dystonia and can be mistaken for non-dystonic tremor, particularly when isolated (14). The diagnosis of dystonia can be missed or delayed in a number of patients with task- and position-specific tremors, particularly primary writing tremor, occupational tremors, or isolated voice tremor, as typical features of dystonia may not develop until many years after onset. Head or voice tremors observed in tremulous forms of cervical dystonia can be very hard to distinguish from essential tremor. In some cases, only family history orientates in favour of the correct diagnosis, particularly if family members are ascertained to have dystonia.

Table 18.1 Aetiological classification of dystonia (11)

◆ <i>Primary pure dystonia</i> Dystonia is the only clinical sign (apart from tremor) and there is no identifiable exogenous cause or other inherited or degenerative disease. Examples are DYT1 and DYT6 dystonias.
◆ <i>Primary dystonia-plus</i> Dystonia is a prominent sign, but is associated with another movement disorder (e.g. myoclonus or parkinsonism). There is no evidence of neurodegeneration. Examples are levodopa-responsive dystonia (DYT5) and myoclonus–dystonia (DYT11).
◆ <i>Primary paroxysmal</i> Dystonia occurs in brief episodes with normality in between. These disorders are classified as idiopathic (often familial, although sporadic cases also occur) and symptomatic due to a variety of causes. Three main forms are known depending on the triggering factor. In paroxysmal kinesigenic dyskinesia (PKD, DYT9) attacks are induced by sudden movement; in paroxysmal exercise-induced dystonia (PED) attacks are induced by exercise such as walking or swimming; and in the non-kinesigenic form (PNKD, DYT8) attacks are induced by alcohol, coffee, tea, etc. A complicated familial form with PNKD and spasticity (DYT10) has also been described.
◆ <i>Heredodegenerative</i> Dystonia is a feature, among other neurological signs, of a heredodegenerative disorder. An example is Wilson disease.
◆ <i>Secondary</i> Dystonia is a symptom of an identified neurological condition, such as a focal brain lesion, or exposure to drugs or chemicals. Examples are dystonia due to a brain tumour, OFF-period dystonia in Parkinson's disease.

Associated features

Dystonia has some unique activation/deactivation features that can be recognized if appropriately looked for and serve as a basis for the diagnosis: *geste antagoniste* (or sensory tricks), mirroring, and overflow. Criteria for identifying these features, when present, have recently been published (8).

Geste antagoniste has been described in patients with different forms of focal dystonia, who reduce or even abolish dystonic postures while making some specific voluntary movements. For example, cranial dystonia patients can apply pressure to the eyebrows or touch the skin beside the eyes to relieve blepharospasm; cervical dystonia patients can place a hand on the side of the face, the chin, or the back of the head, or touch these areas with one or more fingers, to reduce neck contractions; writer's cramp patients can touch the affected arm with the opposite hand. In contrast with the cardinal signs of dystonia, the *geste* is never forceful, but is natural and elegant (8). The mechanism of action of the *geste* is debated; its action is not associated with mechanical correction by counter-pressure (15). A *geste* does not improve non-dystonic essential head tremor, it is uncommon in early post-traumatic dystonia, and it has atypical phenomenology in patients with psychogenic dystonia (8). *Geste* efficacy may diminish as the disease progresses.

Overflow and mirroring are two related clinical phenomena that reveal or enhance dystonia and prove particularly helpful in cases with mild or inconstant phenomenology. Overflow is an unintentional contraction of muscles not primarily involved by dystonia, usually located in neighbouring body sites, which are activated at the peak of dystonic movements (16). For example, a patient with cervical dystonia may have involvement of the unaffected upper limb by occasional spread of dystonia activity. Mirror dystonia occurs on the affected body side when a specific task is performed by the homologous opposite unaffected body part. Usually specific tasks elicit mirror dystonia; they must be identified in order to appreciate this feature. For example, patients with writer's cramp may present mirror dystonia of the dominant hand while writing with the non-dominant unaffected hand (17). Overflow and mirroring are considered a clinical expression of lack of inhibition occurring in dystonia (8).

Diagnostic algorithm

A diagnostic algorithm for identifying the features of primary dystonia has recently been proposed (8). According to this schema, when all the cardinal features of dystonia are observed, the clinical

diagnosis is clearly evidenced by physical examination. Otherwise, at least two associated features must be observed to reach a clinical diagnosis. EMG observation of features associated with dystonia is helpful when physical observation is insufficient (Fig. 18.1).

Epidemiology

The prevalence of primary dystonia is difficult to ascertain, ranging from 2 to 50 cases per million for early-onset primary dystonia, and from 30 to 7320 cases per million for late-onset dystonia. On the basis of the best available prevalence studies, primary dystonia may account for 11.1 per 100 000 early-onset cases in Ashkenazi Jews from the New York area, 60 per 100 000 late-onset cases in Northern England, and 300 per 100 000 late-onset cases in the Italian population aged over 50 (18).

For a number of reasons, the true prevalence of dystonia is probably underestimated. Patients with mild phenotypes (so-called *formes frustes* (19)) may not seek medical advice; those in whom the clinical diagnosis is missed require expert evaluation to resolve diagnostic uncertainty. Conditions that are more common or better known than dystonia often include other movement disorders, such as Parkinson's disease, essential tremor, myoclonus, tics, and psychogenic forms (14).

Aetiology

A genetic predisposition and environmental factors both play a significant role in the aetiology of primary dystonia. Genetic defects are known for only a minority of cases presenting with a pure dystonia phenotype (20). In contrast, dystonia-plus syndromes are better classified genetically (Table 18.2). We describe here only the primary pure dystonia syndromes. Dystonia-plus and paroxysmal dystonias are dealt with in Chapters 19 and 26.

DYT1 dystonia

A common cause of generalized primary pure dystonia is the GAG deletion in the *DYT1* gene encoding the protein TorsinA (21). The disease was originally described among Ashkenazi Jews as having a relatively homogeneous phenotype characterized by early limb-onset generalized dystonia (22). It was later reported that, particularly in Caucasian patients (23), the DYT1 phenotype is broader than originally thought. The 'classical' DYT1 phenotype is characterized by early onset in a limb, and generalization without spread to the craniocervical region (23). In a series of patients with early-onset

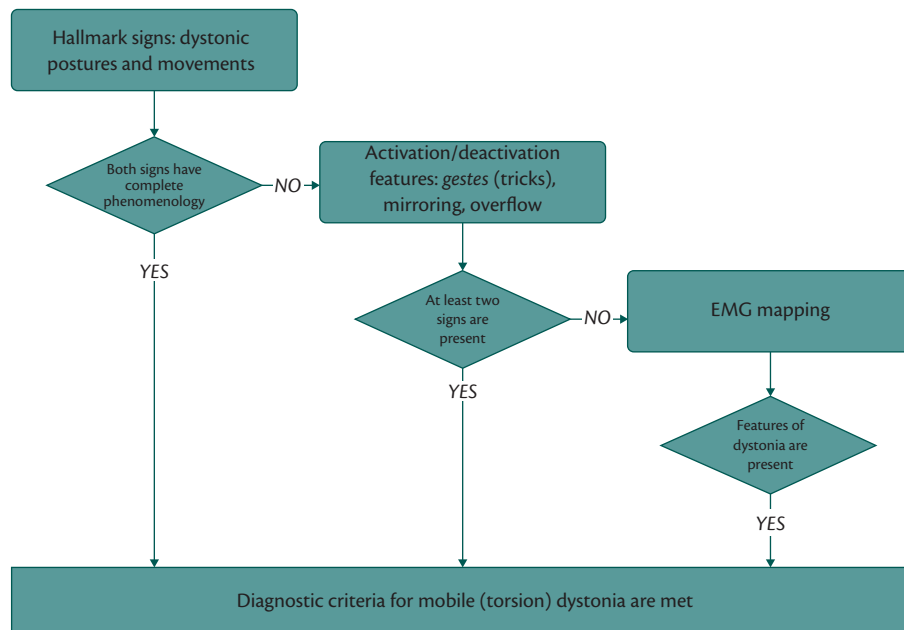


Fig. 18.1 Flowchart for the diagnosis of mobile (torsion) dystonia. This stepped approach allows a clinical diagnostic level to be reached based on objective clinical criteria. (Reproduced with permission from Albanese A, Lalli S. Is this dystonia? *Mov Disord* 2009; 24: 1725–31)

primary dystonia, it has been confirmed that dystonia never starts in the craniocervical region in *DYT1* carriers, although craniocervical sites can be involved at later stages (24). It is remarkable that *DYT1* patients who develop severe generalized involvement can carry out their daily activities with significant adaptation in many cases. Extreme cases have also been observed, ranging from asymptomatic status to craniocervical involvement or even status dystonicus (25–28).

Owing to phenotypic heterogeneity, it is not possible to identify *DYT1* patients based only on their clinical presentation. Five other phenotypes have been described in addition to the classic limb-onset presentation (24, 29): generalized dystonia with craniocervical involvement, more frequent in Europe than in North America (30), generalized myoclonus–dystonia, with a phenotype more severe than observed in *DYT11* myoclonus–dystonia (31), focal dystonia with slow progression and occasional later spread even several years after onset (32, 33); late-onset *DYT1* forms (25), and rarer cases of *DYT1* dystonia with non-limb presentation which may have cervical, laryngeal, or trunk onset (34, 35).

Gene penetrance is believed to be around 30% (21, 27), meaning that the proportion of asymptomatic mutation carriers is higher than that of manifesting patients. This has prompted the search for potential endophenotypes to help identify manifesting as well as non-manifesting *DYT1* carriers. Two potential endophenotypes have emerged: reduction of striatal D2 receptor binding shown by PET studies (36), and higher tactile and visuotactile temporal discrimination thresholds or temporal order judgements (37). These findings need to be confirmed and have not been integrated into a coherent diagnostic protocol.

The *DYT1* gene is named *TOR1A* (21). The disease is caused by a unique mutation that deletes one of a pair of GAG triplets from the carboxyl terminal in TorsinA. This unique *DYT1* haplotype, originally found in Ashkenazi Jews, has also been observed in non-Jewish patients (38) and represents the only pathogenic disease mutation identified in *TOR1A*. An 18 bp deletion has also been found in families with primary dystonia and myoclonus,

but its pathogenicity has not been ascertained (39). TorsinA is a heat-shock and ATP-binding protein and a member of the AAA+ superfamily. The normal protein is widely distributed in many species and is located in the endoplasmic reticulum (40, 41). Immunohistochemical studies have revealed that TorsinA is a constituent of Lewy bodies (42).

DYT6 dystonia

The *DYT6* locus was originally mapped in two Mennonite families with primary pure dystonia and autosomal dominant transmission (43). Mutations in the *THAP1* (Thanatos-associated-domain containing apoptosis-associated protein 1) gene have been found to be responsible for *DYT6* dystonia with an estimated penetrance of approximately 60% (44). In an American series, *THAP1* heterozygous mutations were identified in nine out of thirty-six (25%) *DYT1*-negative families with early-onset non-focal primary dystonia (45). European series have reported a lower mutation frequency with an overall prevalence of 1–2.5% in primary dystonia cohorts from all over Europe (46, 47). The spectrum of *THAP1* mutations includes missense, nonsense, and frame-shift mutations of all three exons.

The *THAP1* phenotype typically presents with early-onset dystonia (age range, 9–49 years) and frequent involvement of the craniocervical area. The motor features often appear in adolescence and may progress rapidly. Speech is commonly affected because of oromandibular or laryngeal involvement (or both). Interestingly, *THAP1* mutations have been recently found in cases with much later onset (fifth or sixth decade) and focal or segmental phenomenology involving the cervical or laryngeal areas (46, 47). This suggests that the gene may also play a pathogenic role in late-onset, focal, or segmental PD.

THAP1 is a member of the family of sequence-specific DNA-binding factors. Its function is still poorly understood; recent studies provided evidence that *THAP1* and *TOR1A* are interconnected in a common pathway (48), because wild-type *THAP1* represses the expression of *TOR1A* (49).

Table 18.2 DYT genotypes associated with dystonias*

Disease (OMIM)	Map position	Gene	Transmission	Phenotype
Pure dystonia				
DYT1 (128100)	9q34	TOR1A	AD	Generalized early-limb-onset dystonia
DYT2 (224500)			AR	Early-onset generalized dystonia with prominent craniocervical involvement
DYT4 (128101)			AD	Whispering dysphonia
DYT6 (602629)	8p11. 21	THAP1	AD	Mixed-type dystonia, early-onset generalized with craniocervical involvement
DYT7 (602124)	18p		AD	Mixed-type dystonia
DYT13 (607671)	1p36. 13–36. 32		AD	Mixed-type dystonia
DYT17 (612406)	20p11.2-q13.12		AR	Segmental or generalized dystonia with severe dysphonia
DTY21 (not assigned)	2q14.3-q21.3		AD	Mixed-type dystonia, late-onset multifocal with craniocervical involvement
Dystonia-plus				
DYT5/DYT14 (128230)	14q22	GCH1	AD	Dopa-responsive dystonia
	11p15.5	TH	AR	Dopa-responsive dystonia
	2p13.2	SPR	AR	Dopa-responsive dystonia
DYT11 (159900)	11q23. 1, 7q21	SGCE	AD	Myoclonus–dystonia
DYT12 (128235)	19q12-q13. 2	ATP1A3	AD	Rapid-onset dystonia–parkinsonism
DYT15 (607488)	18p11		AD	Myoclonus–dystonia
DYT16 (612067)	2q31. 3	PRKRA	AR	Dystonia–parkinsonism
Paroxysmal dystonia				
DYT8 (118800)	2q35	MR1	AD	Paroxysmal non-kinesigenic dyskinesia
DYT9/DYT18 (612126)	1p35-p31. 3	SLC2A1	AD	Paroxysmal exercise-induced dyskinesia
DYT10 (128200)	16p11. 2-q12. 1		AD	Episodic kinesigenic dyskinesia
DYT19 (611031)	16q13-q22. 1		AD	Episodic kinesigenic dyskinesia
DYT20 (611147)	2q31		AD	Paroxysmal exercise-induced dyskinesia
Heredodegenerative				
DYT3 (314250)	Xq13	TAF1	X-linked	Dystonia–parkinsonism

*The gene name is indicated when known; otherwise, the locus is reported.

AD, autosomal dominant; AR, autosomal recessive; ATP1A3, ATPase, Na⁺/K⁺ transporting; GCH1, guanosine triphosphate cyclohydrolase 1; MR1, myofibrillogenesis regulator 1; PRKRA, double-stranded RNA-activated protein kinase; SGCE, ε-sarcoglycan; SLC2A1, solute carrier family 2 (facilitated glucose transporter), member 1; SPR, sepiapterin reductase; TAF1, TATA box-binding protein associated factor; TH, tyrosine hydroxylase; THAP1, thanatos-associated protein; TOR1A, torsin A gene.

THAP1-associated DYT6 dystonia should be considered in patients with early-onset DYT1-negative generalized or segmental dystonia, particularly if cranial involvement is prominent. As a rule, age at onset is higher than in DYT1 dystonia, and the topographic distribution differs between the two forms. The exact prevalence of DYT6 dystonia is still undetermined.

Mapped loci

The DYT7 locus, mapping to the short arm of chromosome 18, was identified in a large German family with an autosomal dominant focal pure dystonia phenotype (50). The mean age of disease onset was 40 years with a prevalent phenotype characterized by focal cervical dystonia. In some patients a segmental distribution has been reported, where cervical dystonia is associated with Meige's syndrome or writer's cramp. No patient had generalized dystonia.

The DYT13 locus was mapped in a large Italian family with prominent craniocervical and upper limb involvement and a pure dystonia phenotype (51, 52). In the majority of cases onset was in infancy or adolescence. Of the eleven definitely affected individuals, two had generalized dystonia with early onset in the upper limb

or the cervical region (53). Disability was mild even in generalized cases. A peculiar feature of the DYT13 phenotype is prominent cervical or upper limb involvement, similarly to the DYT6 phenotype, although the DYT13 family has tested negative for DYT6 mutations.

The DYT15 locus was mapped in a large Canadian kindred, whose thirteen affected members had alcohol-responsive myoclonic dystonia involving the upper limbs, hands, and axial muscles (54).

The DYT17 dystonia locus was mapped in a single consanguineous Lebanese family with three sisters suffering from recessively inherited primary pure dystonia and onset in adolescence (55). The site of onset was cervical, with progression to segmental distribution in two of the sisters and generalization in one. Prominent features were dystonia and dysarthria, unresponsive to levodopa.

The DYT21 locus was recently mapped on chromosome 2 in a family from northern Sweden with sixteen members affected by late-onset pure torsion dystonia. The disease is inherited in an autosomal dominant manner with a penetrance that may be as high as 90%. Age at onset ranges between 13 and 50 years, and the

prevalent phenotype is a multifocal dystonia with prominent craniocervical involvement.

Classified phenotypes

DYT2 is a recessive pure dystonia phenotype originally described in three consanguineous pedigrees of Spanish gypsies. The disease was named 'autosomal recessive dystonia in gypsies' and listed as DYT2 (56, 57). In two of the families the presentation was similar to that of DYT1 dystonia, consisting of early limb onset and progression to generalization; in a third family dystonia presented with prominent oromandibular and cervical involvement (57). A Sephardic Jewish Iranian family with a similar phenotype and autosomal recessive inheritance was later described (58). Three siblings in this family had primary dystonia with limb onset in childhood, and slow progression to generalization with predominant craniocervical involvement. Two patients presented with foot dystonia and gait abnormalities as early features, and all had cervical involvement, facial grimacing, blepharospasm, and upper and lower limb dystonia. Two patients also had dystonic dysphagia. A third family with childhood-onset generalized dystonia and autosomal recessive inheritance also shared the broad DYT2 phenotype (59).

The DYT4 phenotype refers to a large Australian pedigree with twenty affected members and autosomal dominant inheritance (60). Penetrance was complete in all the obligate gene carriers examined; age at onset varied from 13 to 37 years. Many patients presented with 'whispering dysphonia', while others had cervical dystonia. Most patients eventually developed generalized dystonia. Wilson disease co-existed in the same pedigree, but was excluded as a cause of dystonia in the affected individuals (61).

Unclassified phenotypes

A number of scattered pedigrees not carrying the DYT1 mutation have been described. In some of these families, DYT6 dystonia has not been excluded. Linkage studies have not been performed or have not been informative, leaving these pedigrees unmapped.

A non-Jewish American family presented with adult-onset DYT1-negative primary dystonia (62). The disease started in the neck in six cases and in a leg in one. All patients developed cervical dystonia, and language impairment (dysarthria or dysphonia) occurred in five. Four patients developed generalization of symptoms. In a Swedish family transmission was autosomal dominant with a heterogeneous phenotype (63). There was involvement of the face and larynx, and generalization occurred in three of the ten patients. A family from South Tyrol had six affected individuals, four of whom developed generalization approximately 5 years after onset (64). The limbs were involved at onset in all cases except one, who started with cervical dystonia. Upper body involvement was observed in three of the four generalized cases. An Italian family had six affected individuals, one of whom had severe segmental dystonia (65). The prevalent phenotype was an adult-onset craniocervical dystonia with occasional axial involvement but no generalization.

A common phenotype was outlined in a series of forty-three Italian patients with non-DYT1 early-onset dystonia (24). This was characterized by cervical involvement, frequent non-limb onset, a relatively benign course, and uncommon generalization. This finding suggests that these non-DYT1 Italian families may share a common genetic defect. Their features are similar to the DYT6

genotype, although DYT6 gene mutations were excluded in these subjects.

Focal dystonia with onset in adulthood may be the only clinical sign in many patients, who usually have no or mild progression to a segmental pure dystonia. The most frequent forms of dystonia with typical sporadic occurrence that remain genetically unclassified are blepharospasm, spasmodic dysphonia, cervical dystonia, Meige's syndrome, and occupational upper limb dystonia.

Cervical dystonia is the most common of these forms. Different abnormal head positions can be observed, including horizontal head rotation (torticollis), head tilting (laterocollis), head flexion (antecollis), and head extension (retrocollis). These postures can be variably combined depending on the neck muscles involved. Repetitive head jerks can resemble head tremor, but can be differentiated when a directional preponderance and sustainment at peak of movement are observed. Pain occurs in 75% of patients with cervical dystonia (66). Cranial dystonias are less prevalent than cervical forms. Spasmodic dysphonia affects the vocal folds; abnormal adduction, which causes a strained strangled voice, is more common than abduction, in which the voice sounds whispering and breathy.

Patients with blepharospasm have abnormal contractions of the orbicularis oculi muscles. Mild cases are characterized by a simple increase in blink rate and occasional flurries of blinking; in more severe cases forceful eye closure can interfere with vision, leading to functional blindness. In oromandibular dystonia there is abnormal activity in lower facial, tongue, jaw, and pharyngeal muscles that can interfere with speaking or swallowing. Brachial dystonia is a form of focal dystonia that can be primarily, or exclusively, present with writing (writer's cramp).

Segmental dystonia can affect the upper and lower cranial muscles, as in the combination of blepharospasm with oromandibular dystonia, sometimes called Meige's syndrome. In craniocervical dystonia, another type of segmental dystonia, the cranial area is involved together with the neck muscles.

Pathophysiology

Dystonia is characterized by an abnormal co-contraction of agonist and antagonist muscles that is worsened by a selection of task-specific movements and is usually relieved by a selection of sensory tricks. The abnormal co-contraction is thought to be caused by a dysfunction at the spinal or cortical level or both (67). Reciprocal inhibition is the central nervous system process by which a muscle is inhibited when its antagonist is activated. A decreased reciprocal inhibition at different levels of the central nervous system might contribute to the excessive movement seen in dystonia. Dystonic patients may have faulty processing within the inhibitory interactions between antagonist muscles at the sensorimotor cortex level.

Neuroimaging studies have recently provided interesting insights to understanding the pathophysiological mechanisms of primary pure dystonia. Diffusion magnetic resonance studies found signal abnormalities in various brain areas (including corpus callosum, basal ganglia, pontine, and prefrontal cortical areas) in cervical dystonia, writer's cramp, and generalized dystonia, but not in blepharospasm (68–71). Functional MRI studies conducted in patients with blepharospasm (72), writer's cramp (73–75), or upper limb focal dystonia (76) demonstrated

that several deep structures and cortical areas may be activated, depending on the different modalities of examination. Voxel-based morphometry showed an increase in grey matter density or volume in various areas, including the cerebellum, basal ganglia, and primary somatosensory cortex, which might represent plastic changes secondary to overuse (77–81). PET studies have provided information about areas of abnormal metabolism in different types of dystonia and in different conditions (e.g. during active involuntary movement or during sleep), providing insight into the role of cerebellar and subcortical structures compared with cortical areas (82, 83).

Several studies have analysed genetically classified dystonias to investigate functional and morphological changes. Non-DYT1 adult-onset dystonia patients and asymptomatic DYT1 carriers have significantly larger basal ganglia than symptomatic DYT1 mutation carriers, with a negative correlation between severity of dystonia and basal ganglia size in DYT1 patients (84). In DYT6 and DYT1 dystonia patients, D2 receptor availability is reduced in the caudate and putamen and [^{11}C]raclopride binding is also reduced in the ventrolateral thalamus (85). These changes were more pronounced in DYT6 than in DYT1 carriers, without any difference between manifesting and non-manifesting carriers. Several studies have failed to detect neuropathological changes in DYT1 dystonia. In particular, immunohistochemistry of the basal ganglia has not revealed morphological abnormalities (86). More recently, however, brainstem abnormalities were observed in four typical DYT1 patients who had perinuclear inclusion bodies in the mid-brain reticular formation and periaqueductal grey matter. These inclusions stained positively for ubiquitin, torsinA, and the nuclear envelope protein lamin A/C. Similar findings were not reported in genetically unclassified adult-onset primary pure dystonia patients (87). These findings suggest that the underlying molecular pathological mechanisms might differ in different dystonia types. In another study, nigral dopaminergic neurons were found to be larger in the substantia nigra of dystonia patients compared with healthy controls, with no difference between DYT1 and non-DYT1 cases (88).

An emerging line of evidence indicates that dystonia could be a disorder of neuroplasticity. In some susceptible individuals, the mechanisms of neuroplasticity during the acquisition of new motor skills are subtly abnormal. In the presence of such a genetic predisposition, environmental factors, such as repetitive training or peripheral nervous system, injury may trigger an abnormal maladaptive plasticity, which can lead to overt dystonia.

Treatment

There is no aetiological or neuroprotective treatment for primary pure dystonia syndromes. Aetiological therapies are available for some dystonia-plus syndromes of metabolic origin, such as levodopa-responsive dystonia, or non-primary forms, such as Wilson disease. Symptomatic treatments aim to relieve involuntary movements, correct abnormal postures, prevent contractures, reduce pain and embarrassment, and improve function (89). Botulinum toxin is the first-line treatment for most types of focal dystonia. Neurosurgical treatments have an increasing role in the symptomatic treatment plan. Evidence-based treatment guidelines have recently been published by the European Federation of Neurological Sciences (11).

Botulinum toxins

Botulinum neurotoxins (BoNTs) inhibit the vesicular release of acetylcholine at the neuromuscular junction, resulting in a transient localized impairment of neurotransmission. Different forms of type A and one type B BoNT are available for clinical use (90) (Table 18.3).

In properly adjusted doses, BoNTs are an effective and safe treatment for cranial and cervical dystonia (91). According to one systematic review, no conclusions can be drawn on the efficacy of BoNT for different types of spasmodic dysphonia (92), although uncontrolled studies have found this treatment efficacious. BoNT/A is also efficacious for the treatment of writing dystonia (93).

BoNT injections can be performed directly or by EMG- or ultrasound-guided targeting, and there is no consensus on which is the most appropriate practice. In recent years, the results of long-term studies of the efficacy and safety of BoNT/A have become available, new formulations of BoNT/A have been marketed, and new studies of BoNT/B have been performed.

The efficacy and safety profile of BoNT treatments have been evaluated in long-term observational studies. BoNT/A is effective and safe in treating blepharospasm, with long-lasting efficacy for up to 15 years (94). In patients with different dystonia types followed for over 12 years there was no decline of efficacy and the main side effects were muscle weakness in or around the injected region (95). OnabotulinumtoxinA immunogenicity was found to be low after long-term use (96). A meta-analysis found that adverse events are more frequent among children with cerebral palsy than in individuals with other conditions (97). BoNTs are safe when repeated treatments are performed over many years, but doctors and patients should be aware that high cumulative doses may be dangerous, particularly in children.

Systemic treatments

Little evidence-based information is available for other medical treatments for primary dystonia.

Anticholinergic drugs at high dosage are reported to be effective in the treatment of childhood-onset primary or secondary generalized dystonias (98, 99). This therapy is generally well tolerated when the dose is started low and increased slowly. Trihexyphenidyl should be titrated up to a dosage of 30–40 mg/day, but some patients might require up to 60–100 mg/day, although dose-related side effects (e.g. drowsiness, memory difficulty, and urinary retention) might limit its usefulness, especially in adults.

Non-controlled trials are available for the effects of antidopaminergic drugs. Tetrabenazine was effective in one small double-blind randomized crossover study (100). The positive effect of this treatment was confirmed in a large series of patients with different types of movement disorders, including dystonia, followed up retrospectively for a mean duration of 6.6 years (101).

Deep brain stimulation (DBS)

Long-term electrical stimulation of the globus pallidus internus (GPi) is now established as an effective treatment for primary generalized or segmental dystonia (102, 103). A randomized 'sham stimulation-controlled' 6-month trial has shown that bilateral high-frequency stimulation of the GPi is efficacious in reducing

Table 18.3 Main muscles involved and typical BoNT doses in more common focal dystonias

	Ona-BoNT/A	Abo-BoNT/A	Inco-BoNT/A	Rima-BoNT/B
Blepharospasm	Orbicularis oculi: 1.25–2.5U for each site (4 sites)	Orbicularis oculi: 5–10U for each site (4 sites)	Orbicularis oculi 1.25–2.5U for each site (4 sites)	Orbicularis oculi: 50–100U for each site (4 sites)
Oromandibular dystonia	Perioral muscles: 2.5–5U for each site (4–5 sites) Masseter: 15–60U for each side (1–2 sites)	Perioral muscles: 10–20U for each site (2–3 sites) Masseter: 60–240U for each side (1–2 sites)	Perioral muscles: 2.5–5U for each site (4–5 sites) Masseter: 15–60U for each side (1–2 sites)	Perioral muscles: 100–200U for each site (4–5 sites) Masseter: 600–2400U for each side (1–2 sites)
Torticollis	Contralateral sternocleidomastoid: 25–50U for each site (2 sites) Omolateral nuchal muscles: 25–50U for each site (2 sites)	Contralateral sternocleidomastoid: 100–200U for each site (2 sites) Omolateral nuchal muscles: 100–200U for each site (2 sites)	Contralateral sternocleidomastoid: 25–50U for each site (2 sites) Omolateral nuchal muscles: 25–50U for each site (2 sites)	Contralateral sternocleidomastoid: 1000–2000U for each site (2 sites) Omolateral nuchal muscles: 1000–2000U for each site (2 sites)
Laterocollis	Omolateral splenius capitis: 12.5–37.5U for each site (2–3 sites) Omolateral sternocleidomastoid: 6.25–12.5U for each site (2 sites)	Omolateral splenius capitis: 50–150U for each site (2–3 sites) Omolateral sternocleidomastoid: 25–50U for each site (2 sites).	Omolateral splenius capitis: 12.5–37.5U for each site (2–3 sites) Omolateral sternocleidomastoid: 6.25–12.5U for each site (2 sites)	Omolateral splenius capitis: 500–1500U for each site (2–3 sites) Omolateral sternocleidomastoid: 250–500U for each site (2 sites)
Retrocollis	Bilateral splenius capitis: 18.75–50U for each side	Bilateral splenius capitis: 75–200U for each side	Bilateral splenius capitis: 18.75–50U for each side	Bilateral splenius capitis: 750–2000U for each side
Anterocollis	Bilateral scalenus anterior: 40–60U for each side	Bilateral scalenus anterior: 160–240U for each side	Bilateral scalenus anterior: 40–60U for each side	Bilateral scalenus anterior: 1600–2400U for each side
Laryngeal dystonia (adductor type)	Vocal cord (thyroarytenoid muscle): 1.25–2.5U for each side (5–10U if unilateral) Lateral cricoarytenoid: 2.5–5U for each side	Vocal cord (thyroarytenoid muscle): 5U for each side (20 if unilateral) Lateral cricoarytenoid: 10–20U for each side	Vocal cord (thyroarytenoid muscle): 1.25–2.5U for each side (5–10U if unilateral) Lateral cricoarytenoid: 2.5–5U for each side	Vocal cord (thyroarytenoid muscle): 50–100U for each side (200–500U if unilateral) Lateral cricoarytenoid: 100–200 for each side

motor impairment and disability in patients with primary generalized or cervical dystonia (103).

Surgery is indicated after medications or BoNT have failed to provide adequate improvement. There is limited experience for targets other than the GPi (104), such as the thalamus, the subthalamic nucleus (105), and the cerebral cortex (106). Chronic stimulation in dystonia uses higher pulse-widths and voltages than in Parkinson's disease, resulting in earlier battery depletion; replacement may sometimes be needed every 2 years or less. GPi DBS is generally less effective in secondary dystonia. This procedure requires a specialized expertise and a multidisciplinary team, and may be limited by the occurrence of side effects. Other indications are still being explored, such as status dystonicus, task-specific dystonias, camptocormia, secondary hemidystonia, pantothene-kinase-associated neurodegeneration, Lesch–Nyhan disease, and cerebral-palsy-related dystonia–choreoathetosis.

According to a National Institute for Health and Clinical Excellence (NICE) guideline (107), GPi DBS provides marked benefit with improvement of dystonia motor scores (34–88%) and disability scores (40–50%). A meta-analysis using a regression analysis, published in 2006, revealed that longer duration of dystonia correlated negatively with surgical outcome (108). Improvement of dystonia after DBS commonly follows a specific pattern, with phasic (clonic or tremulous) elements improving earlier than tonic

features, with improvement in the latter often developed by weeks or months (109–111). Overall, the most beneficial results with pallidal DBS were reported in children with primary generalized dystonia, particularly in DYT1 dystonia, which improves by 40–90% (112–114). Long-term efficacy was reported to be sustained after more than 5 years of follow-up (115). In patients with cervical dystonia, GPi DBS has so far been used mainly in those who were not thought to be ideal candidates for peripheral denervation, including patients with head tremor and myoclonus or marked phasic movements (116).

Safety aspects which have to be considered include surgery-related complications, stimulation-induced side effects, and hardware-related problems. Chronic high-voltage GPi DBS may induce a parkinsonian gait or bradykinesia in limbs unaffected by dystonia (117, 118). Bilateral pallidal stimulation does not impair cognitive performance (119).

Other neurosurgical procedures

According to the NICE guidelines (120), selective peripheral denervation in cervical dystonia requires specialized expertise, but is safe, with infrequent and minimal side effects, and is indicated exclusively in cervical dystonia. According to EFNS guidelines there is insufficient evidence to use this treatment in primary dystonia, although this procedure may be indicated in patients affected

by secondary dystonia combined with spasticity (91). Intrathecal baclofen has been used in patients with severe generalized dystonia. Since this treatment is complicated by medication-related side effects, it is currently indicated only in patients where secondary dystonia is combined with spasticity (121).

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