

CHAPTER 8

Primary Dystonias

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Historical background

Dystonia was one of the last hyperkinetic disorders to be recognized: the name derives etymologically from a supposed alteration of muscle tone. The term was coined in 1911 by Oppenheim, who observed that muscle tone is *“hypotonic but also characterized by hypertonia and active contractures, which are especially induced by voluntary movements during standing and walking”* [1]. He first stated that dystonia was an organic disease and enriched the clinical observation with some characteristic signs: twisted postures of the limbs and trunk associated with muscle spasms, bizarre alterations in gait, with buckle, bend, and twist of the trunk, rapid jerking and sometimes rhythmic movements, tendency of symptoms to progress until the appearance of fixed postural deformity. He is thought to have observed cases of DYT1 dystonia, as he described the progressive limb and axial involvement in the affected patients.

The hereditary nature of this disorder was mentioned by Flatau and Sterling [2], who also proposed use of the expression *“progressive torsion spasm”* as they believed that the alteration in muscle tone was not the most characteristic clinical sign of this condition.

In the early sixties Denny-Brown identified dystonia as a basal ganglia disease and considered it *“a disturbance of attitude,”* which began with instability of posture, *“with a tendency to patterned*

attitudes that at first were labile and gradually became more fixed” [3]. He described two fundamental patterns: one with flexed arms and extended lower limbs, which he called *“hemiplegic dystonia”* and was considered to be related to putaminal lesions; the other with general flexion, which was associated with damage to the globus pallidum. Following these observations, the term dystonia has also been used to encompass postural abnormalities observed in spastic paralysis or fixed postural abnormalities [3].

The phenomenology of dystonia coincided with the generalised phenotype for many decades, until Marsden and Harrison used the term *“torsion dystonia”* to describe *“a syndrome characterized by dystonic movements and typical posture, regardless of aetiology and related neuropathology”* [4]. In June 1975 an international conference chaired by Stanley Fahn in New York City laid the way to the modern era and recognized the clinical features of focal dystonias [5]. David Marsden’s intuition then provided the intellectual glue for lumping together focal dystonia entities that were previously considered independent nosologic forms (e.g. blepharospasm, torticollis, *“spastic”* dysphonia, and writer’s cramp) [4, 6–9]. 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 twist-*

ing and repetitive movements, or abnormal postures” [10]; later it was recognized that the association of slow tonic posturing with faster (phasic) movements (sometimes resembling tremor) is the clinical hallmark of this movement disorder [10–12].

Classification

The classification of dystonia syndromes has changed over time. Fahn and Eldridge [5] 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, age at disease onset (early vs. adult), distribution of involved body sites (from focal to generalized), and etiology (differentiating idiopathic dystonia syndromes, sporadic or familial, from symptomatic ones) [10, 11]. The first two axes remained unchanged until today, whereas the etiological classification was expanded to include four subgroups of dystonia syndromes: primary, dystonia-plus (i.e. dystonia with parkinsonism or myoclonic jerks), secondary, and heredodegenerative [13].

The recently published European dystonia Guidelines [14] retain the three axes (Box 8.1) and refine the etiological axis distinguishing primary (or idiopathic) dystonia syndromes, heredodegenerative (where dystonia is a feature of a genetic

Box 8.1 Classification of dystonia based on three axes.

By etiology

- **Primary pure dystonia:** 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.
- **Primary dystonia-plus:** dystonia is a prominent sign, but is associated with another movement disorder, for example myoclonus or parkinsonism. There is no evidence of neurodegeneration. For example, DOPA-responsive dystonia (DYT5) and myoclonus-dystonia (DYT11) belong to this category.
- **Primary paroxysmal:** dystonia occurs in brief episodes with normalcy 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) by exercise such as walking or swimming, and in the non-kinesigenic form (PNKD; DYT8) by alcohol, coffee, tea, etc. A complicated familial form with PNKD and spasticity (DYT10) has also been described.
- **Heredodegenerative:** dystonia is a feature, among other neurological signs, of a heredodegenerative disorders. Example: Wilson disease.
- **Secondary:** dystonia is a symptom of an identified neurological condition, such as a focal brain lesion, exposure to drugs or chemicals. Examples: dystonia due to a brain tumour, off-period dystonia in Parkinson disease.

By age at onset

- **Early onset** (variably defined as ≤ 20 –30 years): usually starts in a leg or arm and frequently progresses to involve other limbs and the trunk.
- **Late onset:** usually starts in the neck (including the larynx), the cranial muscles or one arm. Tends to remain localised with restricted progression to adjacent muscles.

By distribution

- **Focal:** single body region (e.g. writer's cramp, blepharospasm)
- **Segmental:** contiguous body regions (e.g. cranial and cervical, cervical and upper limb)
- **Multifocal:** non-contiguous body regions (e.g. upper and lower limb, cranial and upper limb)
- **Generalised:** both legs and at least one other body region (usually one or both arms)
- **Hemidystonia:** half of the body (usually secondary to a structural lesion in the contralateral basal ganglia)

Source: Albanese et al. [14].

disorder characterized by neurodegeneration), and secondary (or symptomatic) syndromes. 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 forms (characterized by intermittent symptoms). Age at onset defines early-onset forms (variably defined as starting before 20–30 years), which usually start in a leg or arm and frequently progress to involve other limbs and the trunk, and adult-onset forms, which usually start in the neck (including the larynx), the cranial muscles or one arm and present limited progression to adjacent muscles. The distribution axis defines forms as: focal (if a single body region is affected), segmental (if contiguous body regions are affected), multifocal (if non-contiguous body regions are affected), and generalized (if dystonia is present in both legs and at least one other body region).

Epidemiology

The prevalence of primary dystonia is difficult to ascertain. The estimates range from 2 to 50 cases per million, for early-onset primary dystonia, and from 30 to 7,320 cases per million for late-onset dystonia. On the basis of the best available prevalence studies, primary dystonia may be 11.1 per 100,000 for early-onset cases in Ashkenazi Jews from New York area, 60 per 100,000 for late-onset cases in Northern England, and 300 per 100,000 for late-onset cases in the Italian population over age 50 [15].

The true prevalence of dystonia is probably underestimated due to a number of reasons. Diagnostic uncertainties and the occurrence of mild phenotypes (so-called *formes frustes*) [16] lead patients with mild symptoms of dystonia, such as writer's cramp, not to seek medical advice. Another related explanation is the delay of the clinical diagnosis, which often requires expert evaluation to be appreciated. Conditions that are more common or better acknowledged than dystonia include other movement disorders (such as Parkinson's disease, essential tremor, myoclonus, tics, psychogenic

forms) or other conditions, such as headache or scoliosis [17].

Phenomenology of primary dystonia

Cardinal features

Following David Marsden's seminal observation [4], 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 (so-called fixed dystonia) [12]. 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 be present with specific voluntary actions (task-specific dystonia).

Dystonic movements may be regular, appearing as tremor (so-called dystonic tremor [18]). When fast and jerky, they may resemble myoclonus. Dystonic tremor may precede clear abnormal posturing thus raising doubts about the actual diagnosis. A tremor similar to essential tremor may occur in dystonia and can be mistaken for non-dystonic tremor, particularly when isolated [17]. 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 develop only 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 contrast to essential tremor involving the head, dystonic head tremor tends to be more irregular, with directional preponderance, often associated with a null point – a position of the head

in which the tremor ceases. In some cases, family history of essential tremor or dystonia may help with the final diagnosis.

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: gestes antagonistes (or sensory tricks), mirroring, and overflow. Criteria for identifying these features, when present, have been published recently [16].

Gestes antagonistes have 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 on the eyebrows or touch the skin at the side of 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. Contrasting with the cardinal signs of dystonia, gestes are never forceful, but natural and elegant [16]. The mechanism of action of the gestes is debated; their action is not associated with a mechanical correction by counter-pressure [19]. It has been observed that gestes do not improve non-dystonic essential head tremor, are uncommon in early post-traumatic dystonia, and have atypical phenomenology in patients with psychogenic dystonia [16]. The 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, and is usually located in neighboring body sites, which are activated at the peak of dystonic movements [20]. For example, a patient with cervical dystonia may have involvement of the unaffected upper limb by the occasional spread of dystonia activity. Mirror dystonia occurs on the affected body side when a

Video 8.1 Primary cervical dystonia

This is a 30-year-old patient who developed focal cervical dystonia one year before the video. A cranial-cervical trauma had occurred 6 months before disease onset. The video shows cervical dystonia with a predominance of posturing and pain. He has a "geste antagoniste" that relieves neck pain and tension while walking.



<http://bit.ly/sMeLwt>

specific task is performed by the homologous opposite unaffected body part. Usually there are specific tasks that 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 [21]. Overflow and mirroring are considered a clinical expression of lack of inhibition occurring in dystonia [16].

Diagnostic algorithm

A diagnostic algorithm for identifying the features of primary dystonia has been proposed [16]. According to this schema when all the cardinal features of dystonia are observed, the clinical diagnosis is plainly achieved 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 (Figure 8.1).

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. To make the clinical picture more complex, dystonia features can be combined or intermixed with other movement disorders in dystonia plus syndromes.

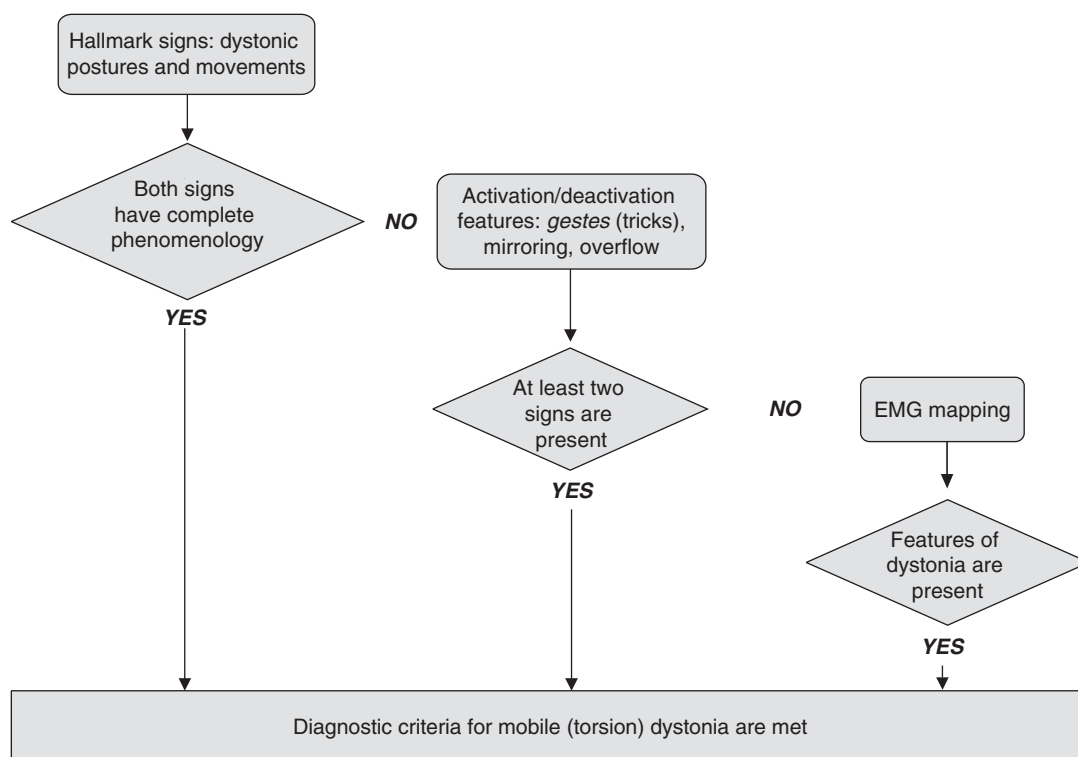


Figure 8.1 Flow chart for the diagnosis of mobile (torsion) dystonia. This stepped approach allows a clinical diagnostic level to be reached on the basis of the criteria listed in Table 8.1. (Reproduced from Albanese and Lalli [16], with permission from Wiley-Blackwell.)

Etiology

It has been shown that both genetic predisposition and environmental factors play a significant role in the etiology of primary dystonia syndromes. An appropriate classification takes into account these two known factors. Genetic defects are known only for a minority of cases presenting with pure dystonia [22]. By contrast, dystonia plus syndromes are by far more precisely classified (Table 8.1). We describe here the most common forms of primary dystonia, without mentioning paroxysmal dystonia syndromes, which are dealt with in Chapter 23.

Genetically classified primary dystonia syndromes

DYT1 dystonia

A common cause of generalized primary pure dystonia is the GAG deletion in the DYT1 gene

encoding the protein Torsin A [23]. The disease was originally described among Ashkenazi Jews with a relatively homogeneous phenotype characterized by early limb-onset generalized dystonia [24]. It was later reported that, particularly in Caucasian patients [25], the DYT1 phenotype is broader than originally thought. The “classical” DYT1 phenotype is characterized by early onset in a limb, generalization without spread to the craniocervical region [25]. In a series of patients with early-onset primary dystonia (PD) it has been confirmed that dystonia never starts in the craniocervical region in DYT1 carriers, although craniocervical sites can be involved at later stages [26]. It is remarkable that DYT1 patients who develop severe generalized involvement may carry out their daily activities with significant adaptation in many cases. Extreme cases have also been observed, ranging from asymptomatic status to

Table 8.1 DYT genotypes associated with dystonias. The gene name is indicated when known; otherwise, the locus is reported.

Disease (OMIM)	Map position	Gene	Transmission	Phenotype
<i>Pure dystonia</i>				
DYT1 (128100)	9q34	<i>TOR1A</i>	AD	Generalized early-limb onset dystonia
DYT2 (224500)			AR	Early-onset generalized dystonia with prominent cranial-cervical involvement
DYT4 (128101)	8p11. 21	<i>THAP1</i>	AD	Whispering dysphonia
DYT6 (602629)			AD	Mixed-type dystonia, early onset generalised with cranial-cervical 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
<i>Dystonia plus</i>				
DYT5/DYT14 (128230)	14q22	<i>GCH1</i>	AD	Dopa-responsive dystonia
	11p15.5	TH	AR	Dopa-responsive dystonia
	2p13.2	SPR	AR	Dopa-responsive dystonia
DYT11 (159900)	11q23. 1, 7q21	<i>SGCE</i>	AD	Myoclonus–dystonia
DYT12 (128235)	19q12–q13. 2	<i>ATP1A3</i>	AD	Rapid onset dystonia parkinsonism
DYT15 (607488)	18p11		AD	Myoclonus–dystonia
DYT16 (612067)	2q31. 3	PRKRA	AR	Dystonia-parkinsonism
<i>Paroxysmal dystonia</i>				
DYT8 (118800)	2q35	MR1	AD	Paroxysmal nonkinesigenic dyskinesia
DYT9 (601042)	1p		AD	Choreoathetosis/spasticity, episodic
DYT10 (128200)	16p11. 2–q12. 1		AD	Episodic kinesigenic dyskinesia
DYT18 (612126)	1p35–p31. 3	<i>SLC2A1</i>	AD	Paroxysmal exercise-induced dyskinesia
DYT19 (611031)	16q13–q22. 1		AD	Episodic kinesigenic dyskinesia
DYT20 (611147)	2q31		AD	Paroxysmal exercise-induced dyskinesia
<i>Heredodegenerative</i>				
DYT3 (314250)	Xq13	TAF1	X-linked	Dystonia-parkinsonism

Abbreviations: 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 boxing-binding protein associated factor; TH, Tyrosine hydroxylase; *THAP1*, Thanatos-associated protein; *TOR1A*, torsin A gene.

craniocervical involvement or even status dystonicus [27–30].

Due 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 classical limb-onset presentation [26, 31]: generalized dystonia with cranial-cervical involvement, more frequent in Europe than in North America [32]; generalized myoclonic-dystonia, with a phenotype more severe

than that observed in DYT11 myoclonus-dystonia [33]; focal dystonia with slow progression and occasional later spread even several years after onset [34, 35]; late-onset DYT1 forms [27]; rarer cases of DYT1 dystonia with non-limb presentation, that may present cervical, laryngeal, or trunk onset [36, 37].

The gene penetrance is estimated to be around 30% [23, 29], meaning that a high proportion of mutation carriers is asymptomatic. This has

prompted the search for potential endophenotypes to help to identify manifesting as well as in non-manifesting DYT1 carriers. Two potential endophenotypes are of interest: reduction of striatal D2 receptor binding shown by PET studies [38], and higher tactile and visuotactile temporal discrimination thresholds or temporal order judgments [39]. These findings need to be confirmed and integrated into a coherent diagnostic protocol.

The DYT1 gene is named *TOR1A* [23]. The disease is caused by a unique mutation that deletes one of a pair of GAG triplets from the carboxyl terminal in Torsin A. This unique DYT1 haplotype originally found in Ashkenazi Jews has also been observed in non-Jewish patients [40] 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 [41]. Torsin A 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 [42, 43].

Video 8.2 Primary dystonia: DYT1 phenotype

This 45-year-old patient has DYT1 dystonia. Dystonia started at age 13 in the right lower limb and impaired walking. The disease progressed with dystonia occurring also at rest spreading to generalization. The video shows rest-type tremor and torsional lower limb instability when standing. Gait is grossly abnormal with both legs affected by dystonia. Severe torsional posturing is visible in the right lower limb. A right striatal toe with mild dystonic movements of the left foot is present at rest. Dystonia during handwriting is also shown.



<http://bit.ly/rzjHUI>

Immunohistochemical studies have revealed that Torsin A is a constituent of Lewy bodies [44].

DYT6 dystonia

The DYT6 locus was originally mapped in two Mennonite families with primary pure dystonia and autosomal dominant transmission [45]. Mutations in the *THAP1* (Thanatos-associated-domain containing, apoptosis-associated protein 1) gene have been found responsible for DYT6 dystonia with an estimated penetrance of approximately 60% [46]. In American series *THAP1* heterozygous mutations were identified in 9 out of 36 (25%) DYT1-negative families with early-onset non-focal PD [47]. European series reported a lower mutation frequency with an overall prevalence of 1.0–2.5% in PD cohorts from all over Europe [48, 49]. 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 to 49 years) and frequent involvement of the cranial-cervical area. The motor features often appear in adolescence and may progress rapidly. Speech is commonly affected, because of oro-mandibular 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 district [48, 49]. 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 [50], because wild type *THAP1* represses the expression of *TOR1A* [51].

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

Video 8.3 Primary dystonia: DYT6 phenotype

This 19-year-old patient carries a point mutation in the THAP1 gene. At age 16 he presented right upper limb dystonia and hand tremor. Two years later he started to have speech difficulties due to occurrence of oromandibular task-specific dystonia while talking. The videotape shows upper limb dystonic tremor (with right hand side prevalence); speech is impaired by lower cranial dystonia.



<http://bit.ly/tZ8Y5B>

DYT5: dopa-responsive dystonia

Dopa-responsive dystonia (DRD) is a neurometabolic disorder classified among the dystonia plus syndromes. Onset is infantile in most cases and two different modes of inheritance have been described. In the autosomal-dominant form (DYT5), heterozygous mutations of GTP-cyclohydrolase I (*GCH1*) cause DRD with reduced penetrance and excellent and sustained response to levodopa. Autosomal-recessive forms (AR-DRD) are caused by homozygous or compound heterozygous mutations of the tyrosine hydroxylase (TH) or the sepiapterin reductase (SPR) gene.

As this is a treatable condition, a particular effort should be made to establish the correct diagnosis early. The most common form is autosomal-dominant DYT5 DRD (also called Segawa's disease). The classical phenotype presents with walking difficulties before 20 years, and progression to segmental or generalized dystonia, sometimes with additional parkinsonian features and sustained response to levodopa [52]. Parkinsonian features consist of rigidity and rapidly-induced fatigue with repetitive motor tasks, which commonly coexist with dystonia, and increased tendon jerks in the affected limb. By 10–15 years after onset, dystonia gradually spreads to involve all the limbs. The resulting

generalized picture typically remains asymmetric and involves the four limbs, being more severe in the legs [53]. One important feature of DRD is the occurrence of diurnal fluctuations: patients are less affected in the morning and more disabled in the evening [54].

Three additional categories of *GCH1*-linked DRD have been recognized [52, 55]: cases with young-onset (<20 years) and episodic dystonia, toe walking and progressive scoliosis; compound heterozygous *GCH1* mutation carriers who develop young-onset severe DRD with early hypotonia, similar to AR-DRD caused by TH mutations; adult-onset DRD manifesting after age 30 years with mild dystonia, resting tremor and non-tremulous parkinsonism. Phenotypic heterogeneity is quite ample and clinical features could not allow the genotype to be predicted even in a large series.

Clinical heterogeneity of DRD is a cause of diagnostic uncertainty. The DRD phenotype can include adult-onset parkinsonism with tremor and levodopa-induced dyskinesias, leading to possible confusion with patients carrying parkin gene mutations, who often develop a dystonic gait disturbance as the initial symptom [56]. The presence of early prominent parkinsonism and severe dyskinesias favours parkin mutations. DAT scan is normal in DRD patients, but not in parkin disease patients [57, 58].

The DRD phenotype can be mistaken for spastic paraparesis because of brisk lower limb reflexes and apparent extensor plantar responses (dystonic toe extension, known as “striatal toe”). Normal motor evoked potentials, unremarkable cranial MRI and positive family history should prompt consideration of a levodopa trial [59]. In one series, up to 24% of DRD patients were misdiagnosed as having cerebral palsy [60]. Particular care should be put in identifying the features of dystonia that lead toward a correct diagnosis.

With screening for gene dosage alterations the rate of detection for *GCH1* mutations is over 80% [61, 62]. If genetic testing of *GCH1* is negative, other genes of the tetrahydrobiopterin and dopamine synthesis pathways, like TH and SPR, should be considered, especially if inheritance is recessive [56, 62]. TH deficiency is the most frequent cause

of AR-DRD and is associated with a broad phenotypic spectrum, ranging from TH-deficient DRD at the mild end to the levodopa-unresponsive infantile parkinsonism or progressive infantile encephalopathy phenotype at the severe end [59]. In mild cases clinical findings may initially be limited to unilateral or asymmetric limb dystonia, postural tremor, or gait “incoordination.” However, progression over time may result in the classic dopa-responsive dystonic gait disorder. Diurnal variation of motor condition may be present, with worsening in the afternoon or the evening [53]. Brain MRI have not revealed structural or signal abnormality in individuals with TH-deficient DRD who have been on treatment for 35 years [63]. Children at the severe end of the spectrum are profoundly disabled by infantile parkinsonism, with onset before 6 months of age, limb rigidity and hypokinesia, developmental motor delay, and truncal hypotonia. Ptosis and/or oculogyric crises are common. These infants are more difficult to treat and unusually prone to side effects (dyskinesias and gastrointestinal complications) from levodopa therapy [53]. Another phenotype associated with TH deficiency presents with progressive infantile encephalopathy, cerebral and cerebellar atrophy; the patients are severely affected and do not respond to levodopa [64].

Response to a therapeutic trial with levodopa orientates towards the diagnosis of DRD [65]. Studies on pterin and dopamine metabolites from cerebrospinal fluid or a phenylalanine loading test have also been suggested as diagnostic complements [66], but their predictive value is still uncertain and both can only be performed in specialized centres. Because DRD is not easily diagnosed, every patient with early-onset dystonia without an alternative diagnosis should have an early levodopa trial to ascertain the diagnosis [14].

DYT11: myoclonus-dystonia

Myoclonus-dystonia (M-D) is a dystonia plus syndrome that also peaks in childhood. The initial symptoms, usually starting in the first two decades, consist of lightning jerks and dystonia mainly affecting the neck and the upper limbs, with a

prevalent proximal involvement. M-D has been described to a greater extent in Chapter 14.

In most cases the presenting symptom is myoclonus, which may be isolated or associated with dystonia. Dystonia is the initial manifestation in about 20% of cases [67].

When present, dystonia is usually mild to moderate, with torticollis or writer’s cramp as the most common manifestations. In patients with onset in infancy, gait disturbance, caused by a mixture of lower limb dystonia and myoclonus, have also been described as the initial presentation [68]. The phenotype generally evolves to cause neck-dominant typical M-D. Large studies suggest that screening for SGCE has low yield in patients with pure dystonia [69]. Family history is frequently remarkable, although sporadic cases have also been reported [70].

Usually M-D is compatible with an active life and a normal lifespan. Both myoclonus and dystonia can worsen at any time during the course of the disease, even in old age, and may spread to previously unaffected body regions [71]. A worsening of myoclonus is not necessarily coupled with a simultaneous worsening of dystonia [72]. Myoclonus and dystonia can improve spontaneously or in relation to treatment [71], a possibility to be considered when planning surgical interventions, such as deep brain stimulation (DBS).

Myoclonus is strikingly alleviated by alcohol in many, but not all, patients [73], leading to a risk of abuse [74]. Neuropsychiatric features have also been reported in several M-D patients, who presented with depression, alcohol abuse, obsessive-compulsive disorder, anxiety/panic/phobic disorders, and psychosis. Impaired verbal learning and memory have also been described in some families [74–76].

Mutations in the epsilon-sarcoglycan gene (*SGCE*, *DYT11*) can be detected in over 50% of patients with a typical M-D phenotype and age at onset below 20 [69, 77–79]. As in DRD, the rate of *SGCE* mutation detection is increased by screening for exon or whole gene deletions (gene dosage) [72]. Although *SGCE* mutations are the commonest known genetic cause, not all individuals with the M-D phenotype carry mutations in the *SGCE* gene,

supporting the genetic heterogeneity of the disorder [77, 80]. Patients with a typical M-D phenotype have been shown to map to 18p11, a locus called DYT15 [81].

DYT12: rapid-onset dystonia parkinsonism

Rapid-onset dystonia parkinsonism (RDP) is a rare dystonia-plus syndrome caused by mutations in the *ATP1A3* gene (DYT12). Onset is in childhood or early adulthood.

The patients develop dystonia, bradykinesia, postural instability, dysarthria and dysphagia over a period ranging from several hours to weeks with triggering factors, such as physical (fever, running, childbirth, excessive alcohol ingestion) or psychological stress in the majority of patients [82]. RDP usually develops over minutes to 30 days and then stabilizes. Delayed worsening of symptoms has been reported to occur in few patients 1–9 years after onset [59]. In addition to rapid onset, other features suggesting RDP are: prominent bulbar involvement and a gradient of dystonia severity with the cranial region being more severely affected than arms and legs. Neither tremor or prominent pain have been described at onset [83].

DYT16: dystonia parkinsonism

This dystonia-plus syndrome is caused by mutations in the *PRKRA* (protein-kinase RNA-dependent activator) gene. The phenotypic spectrum is characterized by early onset with focal dystonia leading to walking and writing difficulties. Progression occurs within few years with facial, cervical, laryngeal dystonia and swallowing difficulties. Pyramidal and psychiatric features are also associated. Brain imaging is unremarkable [84].

Mapped loci

The DYT7 locus, mapping to the short arm of chromosome 18, was identified in a large German family with autosomal dominant focal pure dystonia phenotype [85]. The mean age at 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 cranial dystonia 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 [86, 87]. In the majority of cases onset was in infancy or adolescence. Of the 11 definitely affected individuals, two had generalized dystonia with early onset in the upper limb or in the cervical region [88]. 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, which has nevertheless been excluded in these patients.

The DYT15 locus was mapped in a large Canadian kindred, whose affected 13 members had alcohol-responsive myoclonic dystonia affecting the upper limbs, hands, and axial muscles [81].

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 [89]. 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. Dystonic symptoms did not respond to levodopa.

Video 8.4 Primary dystonia: DYT13 phenotype

This patient is the proband of an Italian family linking to the DYT13 locus. At age 15 he presented abnormal head movements with a rapid (clonic) component and a tonic posturing. The clinical picture slowly progressed to a segmental distribution. At age 54, the patient underwent surgical resection of the right sternocleidomastoid muscle which produced no additional clinical benefit.



<http://bit.ly/rVzffp>

Genetically unclassified dystonia syndromes

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 [90, 91]. In two of the families the presentation was similar to that of DYT1 dystonia, consisting in early limb onset and progression to generalization; in a third family dystonia presented with prominent oromandibular and cervical involvement [91]. A Sephardic Jewish Iranian family with a similar phenotype and autosomal recessive inheritance has been described separately [92]. Three siblings in this family had PD with limb-onset in childhood, and slow progression to generalization with predominant craniocervical involvement. Two patients first developed in-turning of the foot with gait abnormalities, and all had cervical involvement, facial grimacing, blepharospasm, and involvement of the upper and lower limbs. Two patients also had dystonic dysphagia. A third family with childhood-onset, generalized dystonia, and autosomal recessive inheritance also has the DYT2 phenotype [93].

The DYT4 phenotype refers to a large Australian pedigree with 20 affected members and autosomal dominant inheritance [94]. Penetrance was complete in all the examined obligate gene carriers; age at onset varied from 13 to 37 years. Many patients presented with “whispering dysphonia”, others had cervical dystonia. Most patients eventually developed generalized dystonia. Wilson’s disease coexisted in the same pedigree, but was excluded as a cause of dystonia in the affected individuals [95].

Unclassified phenotypes

A number of scattered pedigrees not carrying the DYT1 mutation have been described. In some of these families recently discovered dystonia loci (e.g. DYT6) have 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 PD [96]. The disease started in the neck in 6 cases and in a leg in 1. All

patients developed cervical dystonia, and language impairment (dysarthria or dysphonia) occurred in 5. Four patients developed generalization of symptoms. In another Swedish family transmission was autosomal dominant with a heterogeneous phenotype [97]. There was involvement of the face and larynx, and generalization occurred in 3 of the 10 patients. A family from South Tyrol had 6 affected individuals, 4 of whom developed generalization approximately 5 years after onset [98]. Limbs were involved at onset in all cases but 1, who started with cervical dystonia. Upper body involvement was observed in 3 of the 4 generalized cases. An Italian family had 6 affected individuals, 1 of whom had severe segmental dystonia [99]. The prevalent phenotype was with adult-onset craniocervical dystonia with occasional axial involvement but no generalization.

In a series of 43 Italian patients with non-DYT1 early-onset dystonia a common phenotype was identified [26]. This was characterized by cervical involvement, frequent non-limb onset, relatively benign course and uncommon generalization. This finding suggests that these non-DYT1 Italian families may share a common genetic defect. Their peculiar phenotype is similar to the phenotype associated with the DYT6 genotype, which was ruled out in these subjects.

A focal dystonia with onset in adulthood can 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, oromandibular dystonia, spasmodic dysphonia, cervical dystonia or occupational upper limb dystonia. Figure 8.2 shows the appearance of some focal and generalized dystonia phenotypes.

Cervical dystonia is the most common among these forms. Various abnormal head positions can occur, including horizontal head rotation (torticollis), head tilting (laterocollis), head flexion (anterocollis), or head extension (retrocollis). These postures can be combined variably depending on the neck muscles involved. Pain occurs in 75% of patients with cervical dystonia [100]. Cranial dystonias are less prevalent than cervical forms.

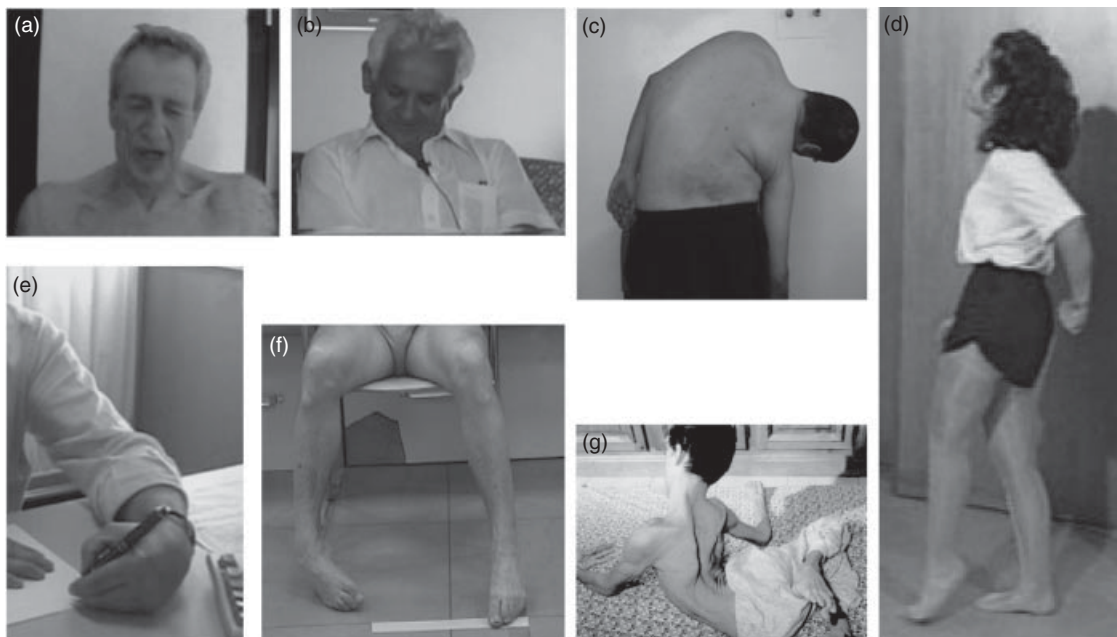


Figure 8.2 Representation of different forms of dystonia: (a) Meige syndrome (still frame from [150]); (b) cervical dystonia (still frame from [88]); (c) axial dystonia; (d) hemidystonia; (e) upper limb dystonia (writer's cramp); (f) lower limbs dystonia in a DYT1 patient; (g) generalized (Oppenheim's) dystonia in a DYT1 patient (reproduced from [28] with permission from Wiley-Blackwell).

Spasmodic dysphonia affects the vocal folds and may result in abnormal adduction, which causes a strained, strangled voice, or, less frequently, it may result in vocal cord abduction, in which the voice sounds whispery and breathy.

Patients with blepharospasm have abnormal contraction of the orbicularis oculi; mild cases are characterized by a simple increase of 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 syndrome. In cranial-cervical dystonia, another type of segmental dystonia, the cranial districts are involved together with the neck muscles.

Pathophysiology

The pathophysiology of dystonia has been reviewed in Chapter 2. The core feature is an abnormal co-contraction of agonists, and antagonists muscles worsened by certain task-specific actions and are sometimes relieved by some sensory tricks. The abnormal co-contraction is thought to be caused by a dysfunction either at the spinal or cortical level or both [101]. Reciprocal inhibition is the central nervous system process in 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. Another research area suggests that dystonic patients may have faulty processing within the inhibitory interactions between antagonist muscles at the sensory-motor cortex level.

An emerging line of evidence indicates that dystonia could be a disorder of neuroplasticity. In some susceptible individuals, during the acquisition of new motor skills, the mechanisms of neuroplasticity are subtly abnormal. In the presence of such predisposition, several environmental factors, such as repetitive training or peripheral nervous system injury, can trigger an abnormal maladaptive plasticity, which can lead to an overt dystonia particularly in patients with a predisposing genetic background [101].

Although primary dystonias are traditionally considered not to be associated with morphological brain abnormalities, voxel-based morphometry studies have shown increase in gray matter density or volume in various areas, including cerebellum, basal ganglia, and primary somatosensory cortex, which might represent plastic changes secondary to overuse [102–106]. Diffusion MRI studies have found signal abnormalities in various brain areas (including corpus callosum, basal ganglia, pontine, brainstem, and prefrontal cortical areas) in cervical dystonia, writer's cramp and primary generalized dystonia, but not blepharospasm [107–110]. It is difficult to reconcile these morphological evidences that may pick up some epiphenomena related to prolonged functional changes in the brain motor systems.

Data on genetically defined forms also provides insights on the neuropathology of primary dystonia. It has been observed that symptomatic DYT1 mutation carriers have a smaller basal ganglia size compared to non-carriers or asymptomatic carriers, and the severity of dystonia correlates negatively with basal ganglia size in DYT1 carriers [111]. A significant reduction in caudate and putamen D2 receptor availability and reduced [^{11}C] raclopride binding has also been described in the ventrolateral thalamus of DYT1 and DYT6 carriers [112]. Other studies failed to observe neuropathological changes in the basal ganglia of DYT1 patients [113], but perinuclear inclusion bodies have been detected in the midbrain reticular formation and periaqueductal gray matter of DYT1 patients [114].

Treatment

There is no etiologic or neuroprotective treatment for primary pure dystonia syndromes. Etiologic remedies are instead available for some dystonia plus syndromes of metabolic origin, such as DRD, or non-primary forms, such as Wilson disease. Symptomatic treatments aim to relieve involuntary movements, correct abnormal posture, prevent contractures, reduce pain and embarrassment, and improve function [115]. Botulinum toxin is the first choice treatment for most types of focal dystonia. Neurosurgical treatments have a growing role in the symptomatic treatment plan. Evidence-based guidelines have been recently published by the European Federation of Neurological Sciences [14].

Etiologic treatments

In metabolic disorders the knowledge of the biochemistry and metabolic pathway involved in the pathogenesis can help to identify etiologic treatments, such as enzyme-replacement therapy to rescue cellular function or systemic delivery of a missing metabolite. A growing number of genes are being found to cause familial forms of dystonia and, consequently, the molecular diagnosis of these disorders is becoming increasingly important.

An etiologic treatment is available for DRD. Reduced activity of *GCH1*, TH, or SPR is thought to cause symptoms by depleting dopamine, consistently with the pronounced therapeutic effect of levodopa, even in patients who have been severely incapacitated for several years [116].

Patients with DRD typically experience a marked long-term benefit with low doses of levodopa [117]. The optimal regimen varies among patients; while some respond magnificently to small doses, others require higher dosages. In the largest available series, clinical benefit was observed at a mean dose of 343.8 mg daily for patients who developed dyskinesias, and 189.1 mg daily for patients without dyskinesias [117]. The overall long-term responsiveness to levodopa was excellent in *GCH1*-DRD and the prescribed doses had to be increased only in a minority of patients. Long-term observations have shown that side

effects such as dyskinesias or motor fluctuations are unlikely to occur [52]. In contrast to patients with *GCH1* mutations, TH-DRD patients may show a delayed and incomplete levodopa response with occurrence of dyskinesias [59].

Botulinum toxins

Botulinum neurotoxins (BoNTs) inhibit the vesicular release of acetylcholine at the neuromuscular junction, resulting in a transient, localized impairment of neurotransmission. Different type A and one type B BoNT are available for clinical use [118].

In properly adjusted doses, BoNTs are effective and safe treatments of cranial and cervical dystonia [119]. According to one systematic review, no conclusions can be drawn on the efficacy of BoNTs for different types of spasmodic dysphonia [120], although uncontrolled studies have found this treatment efficacious. BoNT/A has also been proven efficacious for the treatment of writing dystonia [121].

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

The efficacy and safety profile of BoNT treatments has been evaluated in long-term observational studies. BoNT/A was found to be effective and safe in treating blepharospasm, with long-lasting efficacy up to 15 years of follow up [122]. In patients with different dystonia types followed for over 12 years there was no decline of efficacy and the main side effects consisted in muscle weakness in or around the injected region [123]. Onabotulinumtoxin A immunogenicity was found to be low in long-term use [124]. A meta-analysis found that adverse events are more frequent among children with cerebral palsy than in individuals with other conditions [125]. BoNTs are safe when repeated treatments are performed over many years, but doctors and patients should be aware that excessive cumulative doses may be dangerous, particularly in children.

Systemic treatments

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

Anticholinergic drugs at high dosage are reported to be effective in the treatment of childhood-onset primary or secondary generalized dystonias [126, 127]. 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 per day but some patients might require up to 60–100 mg per 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 on the effects of antidopaminergic drugs. Tetrabenazine was initially found to be effective in a small double-blind randomized cross-over study [128]. The positive effect of this treatment on dystonia was confirmed in a large series of patients with different types of movement disorders, including dystonia, followed up retrospectively for a mean duration of 3.0 years [129].

Deep brain stimulation

Long-term electrical stimulation of the globus pallidum internum (GPi) is now established as an effective treatment for primary generalized or segmental (mainly cervical) dystonia [130, 131]. Surgery is indicated after medications or BoNT have failed to provide adequate improvement. There is limited experience on targets different from the GPi [132] such as the thalamus, the subthalamic nucleus [133], and the cerebral cortex [134]. Chronic stimulation in dystonia uses both higher pulse width and voltage than in PD resulting in earlier battery depletion: replacement may be needed sometimes every 2 years or less. GPi DBS, in general, is less effective in secondary dystonia. This procedure requires a specialized expertise and a multidisciplinary team, and is not without side effects. Other indications are still being explored, such as status dystonicus, task-specific dystonias, camptocormia, secondary hemidystonia, pantothenate kinase-associated neurodegeneration, Lesch-Nyhan and cerebral palsy-related dystonia-choreoathetosis.

According to a National Institute for Clinical Excellence (NICE) guideline [135], GPi DBS provides marked benefit with improvement of dystonia motor scores, ranging between 34 and 88%, and disability scores, between 40 and 50%. A meta-analysis using a regression analysis published in 2006 revealed that longer duration of dystonia correlated negatively with surgical outcome [136]. Improvement of dystonia after DBS commonly follows a specific pattern, with phasic (clonic or tremulous) elements improving earlier than tonic features, the latter often with a delay of weeks or months [137–139]. Overall, the most beneficial results with pallidal DBS were reported in children with primary generalized dystonia, particularly in DYT1 dystonia, which improves in the range of 40 to 90% [140–142]. Long-term efficacy was reported to be sustained after more than 5 years of follow-up [143]. In patients with cervical dystonia, GPi DBS has so far been used primarily in those who were thought not to be ideal candidates for peripheral denervation, including patients with head tremor and myoclonus, or marked phasic movements [144].

Safety aspects which have to be considered include surgery-related complications, stimulation-induced side effects and hardware-related problems. Recently, it was noted that GPi DBS in patients with segmental dystonia may induce a parkinsonian gait or bradykinesia in extremities which were not affected by dystonia at chronic stimulation with high voltage [145, 146]. Bilateral pallidal stimulation does not impair cognitive performance [147].

Other neurosurgical procedures

According to NICE guideline for selective peripheral denervation in cervical dystonia [148], this procedure requires a specialized expertise, it is safe with infrequent and minimal side effects and is indicated exclusively in cervical dystonia. Intrathecal baclofen has been used in patients with severe generalized dystonia. Since this treatment is burdened by medication-related side effects, it is currently indicated only in patients where secondary dystonia is combined with spasticity [149].

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