

24.1 Definition

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.

This recent definition [1] summarizes the hallmark features of dystonia and its recognizable phenomenology with physical signs characterized by a combination of (tonic) postures and (phasic) movements, including tremor. Dystonia has a special relationship with voluntary movements and involves further clinical features, including overflow, mirror dystonia, and *gestes antagonistes* (sensory tricks) (Table 24.1). The full-house phenomenology typically occurs in the isolated non-acquired dystonia syndromes, particularly in recognized genetic forms (e.g.,

DYT1 or DYT6). Clinical recognition becomes forthright when the phenomenology is complete. Conversely, incomplete phenomenology may impede the recognition of dystonia and favor misdiagnosis with other hyperkinetic disorders, such as essential tremor, parkinsonian tremor, and myoclonus [2].

This definition takes into account the broad phenomenology of dystonia that may affect any body part. Body regions involved by dystonia are the upper or lower cranial region, the cervical region, the larynx, the trunk, the upper limbs, or the lower limbs. These different territories may be involved individually or in different combinations. The body distribution may change over time, typically with progression to the involvement of previously uninvolved sites. Although in most cases dystonia combines abnormal movements and postures, some forms of dystonia, such as blepharospasm and laryngeal dystonia, are not associated with postures and rather characterized by focal involuntary contractions that interfere with physiological opening or closing of the eyelids or the larynx.

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24.2 Classification

The current classification of dystonia is based on two axes. Axis I summarizes the clinical features observed in a given patient (Fig. 24.1), whereas axis II classifies etiologies.

Table 24.1 Clinical hallmarks of dystonia

Clinical sign	Depiction
Dystonic (tonic) postures	A body part is flexed or twisted along its longitudinal axis (not available for blepharospasm or laryngeal dystonia). A sensation of rigidity and traction is present in the affected part
Dystonic (phasic) movements, including dystonic tremor	Movement may be fast or slow and may appear as “tremor,” “tic,” “chorea,” or “myoclonus.” The dystonic nature is revealed by recognition of a twisting nature or a pull in a preferred direction, repetitive and patterned attitude (i.e., movements are consistent and predictable); movements are often sustained at their peak to lessen when a given posture (usually opposite to the preferred direction) is identified (“null point”) Dystonic tremor is defined as a spontaneous oscillatory, rhythmical, although often inconstant, patterned movement produced by contractions of dystonic muscles often exacerbated by an attempt to maintain primary (normal) posture. The dystonic tremor may not be relieved by allowing the abnormal dystonic posture to fully develop without resistance (“null point”)
Voluntary action	Purposeful, anticipated, goal-directed movement produced by will. Dystonia is typically influenced by voluntary movement or voluntarily maintained posture, as in antigravity support
Overflow dystonia	Involuntary muscle contraction which accompanies, ipsilaterally or contralaterally, the dystonic movement or dystonic posture but is anatomically distinct from. It commonly occurs at the peak of dystonic movements or postures
Mirror dystonia	Unilateral involuntary posture or movement that is the same or similar in character to a dystonic feature. Mirror dystonia can be elicited in the unaffected or less severely affected body side by dystonia during repetitive tasks of the most affected body side. Typical tasks that can be performed to elicit this sign include finger sequence, writing, or movements resembling piano playing. Mirror dystonia may be present in all limbs, but are most common in the upper limbs, especially the hands
Sensory tricks or gestes antagonistes	Voluntary actions that specifically correct the abnormal posture or alleviate the dystonic movements. Alleviation of dystonia occurs during the geste movement, usually soon after its start and may last for as long as the geste or slowly reverses spontaneously before its end. These are usually simple movements (“gestes”) involving, or directed to, the body region affected by dystonia, but not consisting in a forceful opposition to the phenomenology of dystonia. The geste movement does not push or pull the affected body part, but simply touches it (“sensory trick”) or accompanies it during alleviation of dystonia

24.2.1 Axis I. Clinical Characteristics

The clinical characteristics describe the phenomenology of dystonia in a given patient. Classification along the first axis is primarily aimed to facilitate clinical recognition, diagnosis, and treatment. Once a patient is classified according to this axis, the identification of the clinical characteristics of dystonia and of the associated features defines the syndromic pattern and helps clinical orientation among the diverse presentation and associations of dystonia. Five descriptors are utilized to specify clinical characteristics: age at onset, body distribution, temporal pattern, coexistence of other movement disorders, and other neurological manifestations.

Classification by age at onset distinguishes five age groups, infancy (birth to 2 years), childhood (3–12 years), adolescence (13–20 years), early adulthood (21–40 years), and late adulthood (>40 years), with the major goal to aid diagnostic testing and determining prognosis. For example, dystonia that begins in childhood is more likely to have a discoverable cause and more likely to progress from focal to generalized. For example, dystonia that emerges during infancy, particularly the first year of life, has a very high probability of being due to an inherited metabolic disorder with specific diagnostic implications and grave prognostic consequences [3]. Dystonia that emerges between 2 and 6 years of age might be more consistent with dystonic

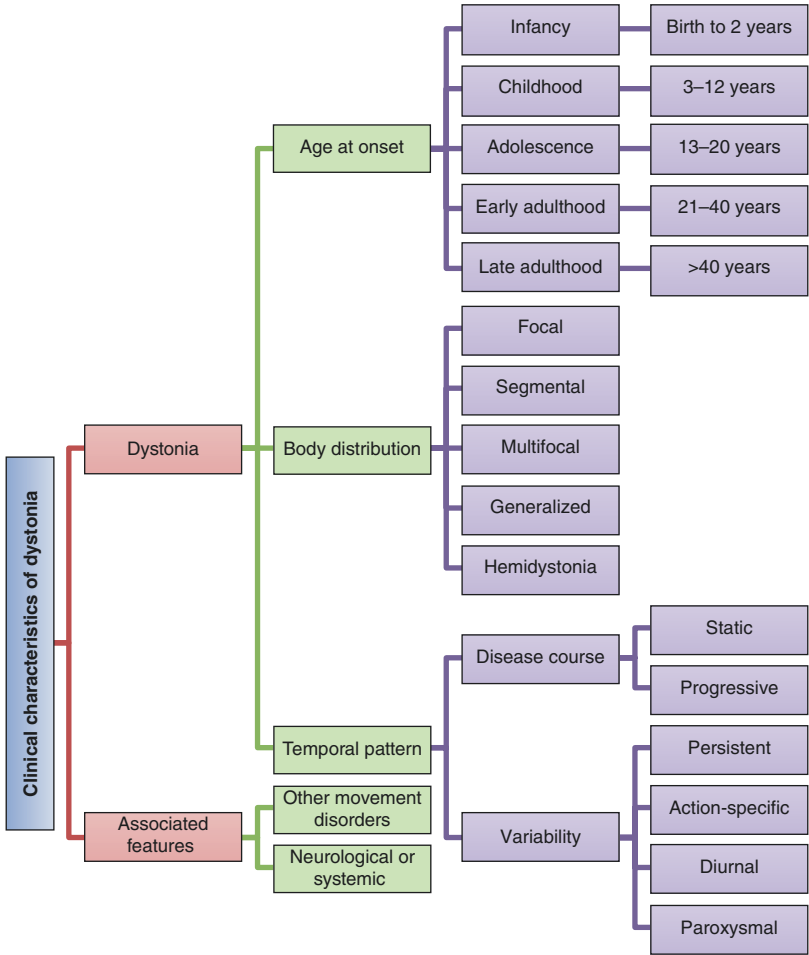


Fig. 24.1 Classification of dystonia along axis I allows to describe the clinical characteristics of dystonia observed in dystonia syndromes. This scheme provides a logical organization of the clinical features that need to be evaluated. If

there are no associated movement disorders or systemic manifestations, dystonia is defined “isolated.” Otherwise it is “combined” with another movement disorder or “associated” with neurological or systemic manifestations

cerebral palsy, especially if it follows a period of developmental motor delay. Other dystonia syndromes, such as dopa-responsive dystonia, tend to emerge between 6 and 14 years of age. Finally, sporadic focal dystonia usually emerges after 50 years of age.

Considering the body regions affected, dystonia may be focal (e.g., blepharospasm, oromandibular dystonia, cervical dystonia, laryngeal dystonia, and writer’s cramp), segmental if two or more contiguous body regions are affected (e.g., blepharospasm with lower facial and jaw or tongue involvement or bi-brachial dystonia), multifocal if two noncontiguous or more (con-

tiguous or not) body regions are involved, or generalized when the trunk and at least two other sites are involved. Hemidystonia is restricted to one body side (typical examples of hemidystonia are due to acquired brain lesions in the contralateral hemisphere). This type of classification has important implications for diagnosis and therapy. For example, the diagnostic considerations in adult-onset focal dystonia are very different from those in young-onset generalized dystonia. The treatment of choice for focal and segmental dystonias involves botulinum neurotoxins, while for generalized dystonias more often involves medications or surgery.

The temporal pattern is an important clinical characteristic that facilitates diagnosis and treatment choices. Important temporal characteristics are related to disease course or variability. The disease course can be either static or progressive. This terminology is particularly used by pediatric neurologists, but it also suits adult cases. In addition, variability provides descriptors on the occurrence of dystonia through the day and can have four different patterns: persistent (dystonia that persists to approximately the same extent throughout the day); action specific (dystonia that occurs only during a particular activity or task); diurnal fluctuations (dystonia fluctuates during the day, with recognizable circadian variations in occurrence, severity, and phenomenology); and paroxysmal (sudden self-limited episodes of dystonia usually induced by a trigger with return to preexisting neurological state). Paroxysmal dystonia should be distinguished from dystonia always triggered by the same activity or action (i.e., task-specific dystonia). In paroxysmal dystonia, the same trigger on different occasions might or might not induce an attack, whereas in action dystonia (including task-specific dystonia), the same motor activity will predictably induce dystonia. Paroxysmal dystonia typically lasts after the trigger has ended, while action (or task-specific) dystonia is no longer evident when the inducing action is completed.

Another important clinical descriptor of dystonia is related to its occurrence in isolation (i.e., dystonia is the only motor feature, with the exception of tremor) or in combination with other movement disorders (such as myoclonus, parkinsonism, etc.). The resulting syndromes may give rise to recognizable associations, such as isolated dystonia or dystonia with myoclonus, parkinsonism, other movement disorders, etc. The term “isolated” or “combined” refers to the phenomenology and does not carry implications about the underlying etiology. In combined forms, dystonia does not necessarily have to be the predominant movement disorder and may not be the prominent motor phenomenology (e.g., foot dystonia in Parkinson disease, mild dystonic features in myoclonus-dystonia).

A relevant step for characterizing dystonia syndromes is outlining the presence or absence of other neurologic or systemic features associated to dystonia. For example, cognitive decline is typically observed in degenerative or progressive dystonia syndromes. Wilson disease is a disorder where dystonia is typically combined with other neurological or psychiatric symptoms and liver disease [4].

24.2.2 Axis II. Etiology

The second axis addresses etiology which is an evolving area as the etiology of many forms of dystonia is still not fully understood. Two complementary characteristics have been recognized as useful for the etiological classification: identifiable anatomical changes and pattern of inheritance. Anatomical causes can be investigated using brain imaging or by pathology. Evidence of degeneration, either at the gross, microscopic, or molecular level, provides a useful means to discriminate subgroups of dystonia into degenerative forms (i.e., progressive structural abnormality, such as neuronal loss), static lesions (i.e., nonprogressive neurodevelopmental anomalies or acquired lesions), and no evidence of degeneration or structural lesion. Pattern of inheritance differentiates inherited (e.g., autosomal dominant, autosomal recessive, X-linked recessive, mitochondrial) from acquired conditions due to a known specific cause (e.g., perinatal brain injury, drugs, vascular, or psychogenic) by means of metabolic, genetic, or other tests. If there is no known cause of dystonia, this is classified as idiopathic, namely, sporadic or familial. Many cases of focal or segmental isolated dystonia with onset in adulthood fall in this category. The most common forms of focal dystonia can have sporadic or familial occurrence.

Inherited dystonias are of proven genetic origin. Dystonia genes are listed with different coding systems, such as the DYT_s, the PARK_s, the PNKD_s, or with non-systematic acronyms. The DYT listing, originally created to encompass the monogenic dystonia syndromes, cannot be considered as comprehensive or exhaustive at present [5, 6] (Table 24.2).

Table 24.2 Synopsis of the most common genetic forms of dystonia

Disease (OMIM) ^a	Gene/locus ^b	Main phenomenology	Transmission ^c
<i>Isolated dystonia</i>			
DYT1 (128100)	TOR1A	Generalized childhood limb-onset dystonia	AD
DYT2 (224500)	None	Childhood/early adulthood-onset generalized dystonia with prominent cranial-cervical involvement	AR
DYT4 (128101)	TUBB4	Adolescence/early adulthood-onset focal, segmental, generalized dystonia with prominent laryngeal involvement (whispering dysphonia)	AD
DYT6 (602629)	THAP1	Adolescence/early adulthood-onset mixed-type dystonia	AD
DYT7 (602124)	18p	Adult-onset focal dystonia	AD
DYT13 (607671)	1p36.13–36.32	Childhood/early adulthood-onset mixed-type dystonia	AD
DYT17 (612406)	20p11.2–q13.12	Adolescent-onset segmental or generalized dystonia with severe dysphonia	AR
DYT21 (614588)	2q14.3–q21.3	Adolescence/adult-onset mixed dystonia	AD
DYT23 (614860)	CIZ1	Adolescence/adult-onset cervical dystonia	AD
DYT24 (615034)	ANO3	Childhood/adult-onset craniocervical, segmental dystonia	AD
DYT25 (615073)	GNAL	Childhood/adult-onset craniocervical, segmental, generalized dystonia	AD
<i>Combined dystonia</i>			
DYT5 (128230)	GCH1	Childhood-onset dopa-responsive dystonia	AD
THD (605407)	TH	Infancy/childhood-onset dopa-responsive dystonia	AR
SPR (612716)	SPR	Dopa-responsive dystonia	AR
DYT11 (159900)	SGCE	Childhood/adolescence-onset myoclonus-dystonia	AD
DYT15 (607488)	18p11	Myoclonus-dystonia	AD
RDP (128235)	ATP1A3	Childhood/adolescence rapid-onset dystonia-parkinsonism	AD
DYT3 (314250)	TAF1	Adult-onset dystonia-parkinsonism	XR
DYT16 (612067)	PRKRA	Childhood/adolescence-onset dystonia-parkinsonism	AR
DTDS (613135)	SLC6A3	Childhood/adult-onset parkinsonism-dystonia	AR
PARK2 (602544)	PRKN	Childhood/early adulthood-onset parkinsonism with limb dystonia	AR
PARK6 (605909)	PINK1	Childhood/late adult-onset parkinsonism with limb dystonia	AR
PARK7 (606324)	DJ1	Childhood/early adulthood-onset parkinsonism with limb dystonia	AR
PNKD1 (118800)	MR1	Infancy/childhood-onset paroxysmal non-kinesigenic dystonia-choreoathetosis	AD
PKD2 (611031)	16q	Childhood/adolescence-onset paroxysmal kinesigenic dystonia-choreoathetosis	AD
<i>Dystonia with other neurological or systemic manifestations</i>			
PNKD2 (611147)	2q31	Childhood/late adult-onset paroxysmal non-kinesigenic dystonia mainly of hands and feet, possible migraines and seizures	AD

(continued)

Table 24.2 (continued)

Disease (OMIM) ^a	Gene/locus ^b	Main phenomenology	Transmission ^c
GLUT1DS2 (612126)	SLC2A1	Childhood-onset paroxysmal exercise-induced dystonia-choreoathetosis with or without epilepsy and/or hemolytic anemia	AD
PKD1 (128200)	PRRT2	Childhood/adolescence-onset paroxysmal kinesigenic dystonia-choreoathetosis and infantile convulsions	AD
AT (208900)	ATM	Childhood-onset cerebellar ataxia, oculocutaneous telangiectases, choreoathetosis, dystonia, myoclonus, oculomotor abnormalities, seizures, short stature, delayed puberty, diabetes mellitus, lymphocytopenia, immune defects, predisposition to neoplasia, and sinopulmonary infections. AT variant with isolated dystonia may be present	AR
CHAC (200150)	VPS13A	Adult-onset parkinsonism, orofacial dyskinesias, dystonia, choreoathetosis, tics, seizures, hyporeflexia, psychosis, possible dementia, acanthocytes, increased creatine kinase	AR
CLF (204200)	CLN3	Childhood-onset cerebral atrophy, macular degeneration, optic atrophy, retinitis pigmentosa, mental retardation, dementia, parkinsonism, myoclonus, cerebellar signs, seizures, concentric hypertrophic cardiomyopathy	AR
DDS (304700)	TIMM8A	Childhood-onset progressive deafness, dystonia, spasticity, mental retardation	XR
DPRLA (125370)	ATN1	Childhood/adult-onset cerebellar ataxia, choreoathetosis, myoclonus, dementia, seizures	AD
FC (230000)	FUCA1	Infancy-onset progressive psychomotor retardation, seizures, neuropathy, spastic quadriplegia, angiokeratoma, coarse facial features, dysostosis multiplex, hearing loss, cardiomegaly, hepatomegaly, splenomegaly, increased urine oligosaccharides, alpha-L-fucosidase deficiency	AR
GA (231670)	GCDH	Infancy-onset encephalopathy, choreoathetosis, dystonia, opisthotonus, spastic diplegia, hepatomegaly, glutaric aciduria, glutaryl-CoA dehydrogenase deficiency, metabolic acidosis, ketonemia, ketonuria, hypoglycemia	AR
HD (143100)	IT-15	Childhood/adult-onset chorea, dystonia, dementia, behavioral disorders, abnormal eye movement; parkinsonism, seizures, ataxic gait (juvenile form)	AD
HDL2 (606438)	JPH3	Adult-onset chorea, dystonia, parkinsonism, dementia	AD

Table 24.2 (continued)

Disease (OMIM) ^a	Gene/locus ^b	Main phenomenology	Transmission ^c
LHON (535000)	Several genes	Childhood/adult-onset optic atrophy, tremor, dystonia, ataxia, neuropathy, cardiac arrhythmia	M
LNS (300322)	HPRT	Mental retardation, motor delay, spasticity, choreoathetosis, dystonia, parkinsonism, self-injurious behavior, hyperuricemia, hyperuricosuria	XR
LS (256000)	Several genes	Infancy/childhood-onset, rapid progression, clinical heterogeneity	M or AR
MLD (250100)	ARSA	Infantile, juvenile, and adult forms with clinical heterogeneity	AR
NFP (606159)	FTL	Neurodegeneration with brain iron accumulation type 3	AD
NPC1 (257220)	NPC1	Infantile, juvenile, or adult forms with clinical heterogeneity. Mental retardation, motor delay, spasticity, ataxia, loss of speech, seizures, myoclonic jerks, dystonia, vertical supranuclear gaze palsy, dementia, and psychiatric manifestations, hepatosplenomegaly, cholestatic jaundice	AR
NPC2 (607625)	HE1	Variable age of onset and phenotype. Developmental delay, loss of speech, mental deterioration, dementia, psychosis, spasticity, dystonia, seizures, cerebellar ataxia, cataplexy, vertical supranuclear gaze palsy, hepatosplenomegaly, pulmonary involvement	AR
PARK14	PLA2G6	Neurodegeneration with brain iron accumulation type 2	AR
PKAN (234200)	PANK2	Neurodegeneration with brain iron accumulation type 1	AR
PMD (312080)	PLP1	Infancy-onset progressive pyramidal and cerebellar signs, optic atrophy, rotary nystagmus, “rolling” head tremor, dystonia, choreoathetosis, parkinsonian, mental retardation, psychomotor delay or deterioration	XR
RTT (312750)	MECP2	Mental retardation, motor delay, autism, seizures, spasticity, ataxia, dystonia, autistic behavior, ECG, respiratory and autonomic abnormalities	XD
SCA17 (607136)	TBP	Adolescence/early adulthood-onset ataxia, parkinsonism, dystonia, chorea, myoclonus, ocular movement abnormalities, seizures, dementia, psychiatric symptoms	AD
SCA3 (109150)	ATXN3	Adult-onset ataxia, spasticity, parkinsonism, dystonia, ocular movement abnormalities, neuropathy, bladder disturbances	AD
SCA6 (183086)	CACNA1A	Adult-onset ataxia, chorea, spasticity, dystonia, ocular movement abnormalities	AD

(continued)

Table 24.2 (continued)

Disease (OMIM) ^a	Gene/locus ^b	Main phenomenology	Transmission ^c
TSD (272800)	HEXA	Infancy-onset paralysis, psychomotor degeneration, dementia, seizures, blindness, Gm2-ganglioside accumulation, hexosaminidase A deficiency	AR
WD (277900)	ATP7B	Tremor, dystonia, parkinsonian features, dementia, visceral and skeletal abnormalities, copper abnormalities, Kayser-Fleischer ring	AR

The gene name is indicated whenever possible; otherwise, the locus is reported

^aAbbreviations: *AT* ataxia-telangiectasia, *CHAC* choreoacanthocytosis, *CLF* ceroid-lipofuscinosis, *DDS* dystonia-deafness syndrome, *DPRLA* dentatorubral-pallidoluysian atrophy, *DTDS* dopamine transporter deficiency syndrome, *GA* glutaricacidemia, *GLUT1DS2* GLUT1 deficiency syndrome 2, *FC* fucosidosis, *HD* Huntington's disease, *HDL2* Huntington-like disease type 2, *LHON* Leber hereditary optic neuropathy, *LNS* Lesch-Nyhan syndrome, *LS* Leigh syndrome, *MLD* metachromatic leukodystrophy, *NFP* neuroferritinopathy, *NPC1* Niemann-Pick type C1, *NPC2* Niemann-Pick type C2, *PARK2* Parkinson disease 2, *PARK6* Parkinson disease 6, *PKAN* pantothenate kinase-associated neurodegeneration, *PKD1* paroxysmal kinesigenic dyskinesia 1, *PKD2* paroxysmal kinesigenic dyskinesia 2, *PMD* Pelizaeus-Merzbacher disease, *PNKD1* paroxysmal non-kinesigenic dyskinesia 1, *PNKD2* paroxysmal non-kinesigenic dyskinesia 2, *RDP* rapid-onset dystonia-parkinsonism, *RTT* Rett syndrome, *SPR* sepiapterin reductase deficiency, *THD* tyrosine hydroxylase deficiency, *TSD* Tay-Sachs disease, *WD* Wilson disease

^bAbbreviations: *ARSA* arylsulfatase A, *ATM* ataxia-telangiectasia mutated gene, *ATN1* atrophin 1, *ATPIA3* ATPase, Na⁺/K⁺ transporting, *ATP7B* ATPase, Cu⁺⁺-transporting beta polypeptide, *ATX3* ataxin-3, *CACNA1A* calcium channel, voltage-dependent, *p/q* type alpha-1a subunit, *CLN3* CLN3 gene, *DJ1* oncogene DJ1, *FUCA1* alpha-L-fucosidase 1, *FTL* ferritin light chain, *GCH1* guanosine triphosphate cyclohydrolase 1, *GCDH* glutaryl-CoA dehydrogenase, *HE1* epididymal secretory protein, *HEXA* hexosaminidase A alpha polypeptide, *HPRT* hypoxanthine guanine phosphoribosyl-transferase 1, *IT-15* important transcript 15 (huntingtin), *JPH3* junctophilin 3, *MECP2* methyl-CpG-binding protein 2, *MRI* myofibrillogenesis regulator 1 gene, *NPC1* Niemann-Pick type C1 gene, *PANK2* pantothenate kinase 2, *PRKN* parkin, *PRKRA* double-stranded RNA-activated protein kinase, *PRRT2* proline-rich transmembrane protein 2, *PLA2G6* phospholipase A2 group VI, *PLP1* proteolipid protein 1, *SLC2A1* solute carrier family 2 (facilitated glucose transporter), member 1, *SPR* sepiapterin reductase deficiency, *SGCE* e-sarcoglycan, *TAF1* TATA boxing-binding protein associated factor, *TBP* TATA box-binding protein, *TH* tyrosine hydroxylase, *THAP1* thanatos-associated protein, *TIMM8A* translocase of inner mitochondrial membrane 8, *TOR1A* torsin A gene, *VPS13A* vacuolar protein sorting 13

^cTransmission: *AD* autosomal dominant, *AR* autosomal recessive, *M* mitochondrial, *XR* X-linked recessive

The most common forms of inherited dystonias are, among the autosomal dominant forms, DYT1, DYT5, DYT6, DYT11, rapid-onset dystonia-parkinsonism (DYT12), neuroferritinopathy (NBIA3), dentatorubral-pallidoluysian atrophy, and Huntington disease. The most common forms of autosomal recessive inherited dystonias encompass Wilson disease, PKAN (NBIA1), PLAN (NBIA2), and type 2 juvenile Parkinson disease (PARK2), and various metabolic disorders. Inherited dystonia with X-linked transmission encompass forms such as Lubag (DYT3), Lesch-Nyhan syndrome, and Mohr-Tranebjærg syndrome. Finally, mitochondrial forms, such as Leigh syndrome or Leber optic atrophy and dystonia, also give rise to inherited dystonias.

The most common idiopathic forms are the isolated focal dystonias that usually have adult-onset and limited tendency to spread. Cervical dystonia (also called “torticollis”) involves the cervical muscles, resulting in abnormal head, neck, and shoulder positions [7]; cranial dystonia may affect the orbicularis oculi (“blepharospasm”) and is often accompanied by contractions of the surrounding muscles, such as the procerus and the corrugator [8]; oromandibular dystonia affects the mouth, tongue, or the jaw in isolation or in combination [9, 10]; laryngeal dystonia (also known as “spasmodic dysphonia”) affects phonatory muscles [11]; “occupational cramps” (e.g., writer’s cramp, musician’s cramp) are task-specific forms of dystonia affecting the upper limb [12]. The syndromes of late (adult)-

onset isolated focal dystonia are usually sporadic without an identifiable cause and rarely progress to generalization, although they can spread to involve contiguous body regions (segmental distribution).

The most common forms of acquired dystonias are due to perinatal brain injury (dystonic cerebral palsy, delayed-onset dystonia), infection (viral encephalitis, encephalitis lethargica, subacute sclerosing panencephalitis, human immunodeficiency virus infection, tuberculosis, syphilis, etc.), drug (levodopa and dopamine agonists, neuroleptics (dopamine receptor-blocking drugs), anticonvulsants, and calcium channel blockers), toxic (manganese, cobalt, carbon disulfide, cyanide, methanol, disulfiram, and 3-nitropropionic acid), vascular (ischemia, hemorrhage, and arteriovenous malformation including aneurysm), neoplastic (brain tumor, and paraneoplastic encephalitis), brain injury (head trauma, brain surgery including stereotactic ablations, and electrical injury), and psychogenic (functional).

24.3 Diagnosis

The diagnosis of dystonia is clinical, as there is no specific diagnostic test allowing to confirm the diagnosis. Therefore, expert clinical examination is warranted [13]. The diagnosis is made by searching for the cardinal physical signs that constitute the hallmark of dystonia and are summarized in Table 24.1. These signs have to be looked for in all movement disorders, either fast or slow, also when the immediate clinical impression is that of a “tremor,” “tic,” “chorea,” or “myoclonus.” In this diagnostic process, disorders that may mimic dystonia (pseudodystonia), such as those due to spasms, orthopedic, or neuromuscular disorders, should be ruled out [1]. In fact, these conditions result in abnormal movements, postures, or spasm, which are not associated with the specific phenomenology of dystonia.

Although the recognition of dystonia is based on clinical features and neurophysiological tests are not routinely recommended for the diagnosis,

electromyography (EMG) mapping from various muscles may contribute to the clinical assessment by showing some characteristic features of dystonia [13]. EMG can complement clinical observation and can be useful to distinguish the three types of abnormal activation (tonic, phasic, and tremulous) that correspond to the homonymous clinical features [14], to detect features of dystonia such as co-activation of agonist muscles with greater detail than allowed by visual inspection, to differentiate different types of tremors from myoclonus and dystonia, and finally to identify the muscles involved and the actual disease topography [15]. Therefore, the observation of EMG abnormalities typical of dystonia is helpful when the clinical features are considered insufficient to the diagnosis [16].

Once a diagnosis of dystonia has been made, the next step is to delineate the clinical dystonia syndrome [17]. A careful delineation of the syndromic pattern, along with neuroimaging characteristics, is important because it aids in narrowing down the long list of potential etiologies for more targeted diagnostic testing.

For patients with isolated dystonia, the investigation process depends on the age at onset, the body distribution, and whether there are affected family members. In adults with focal or segmental dystonia only, no diagnostic tests are required because they usually are unrevealing [18]. In adults with hemidystonia or generalized dystonia, neuroimaging is useful because the likelihood of disclosing a structural cause is higher. The diagnostic approach in younger individuals with isolated dystonia is quite different, because there is a much higher likelihood of disclosing a cause [19]. Neuroimaging is important for all early-onset cases, regardless of body distribution. Genetic testing may be performed after establishing the clinical diagnosis. The EFNS guidelines provide indications for performing genetic testing [13]. TOR1A testing is recommended for patients with early-onset limb isolated dystonia and in those with an affected relative with early-onset dystonia. THAP1 testing is recommended in early-onset or familial cases with craniocervical dystonia or after

exclusion of DYT1. Individuals with early-onset myoclonus should be tested for mutations in the SGCE gene. If direct sequencing of the SGCE gene is negative, additional gene dosage is required to improve the proportion of mutations detected. A levodopa trial is warranted in every patient with early-onset isolated dystonia without an alternative diagnosis. In sporadic adult-onset isolated dystonias, the chance of finding a genetic cause is less than 2%, so genetic testing usually is not cost-effective, unless there are other affected family members [19].

For all patients in whom dystonia is combined with other neurologic or systemic features, some additional investigation work-up is warranted, regardless of the age at onset or body distribution. The laboratory work-up depends on the nature of the associated features and the age at onset. More than 100 different syndromes with combined dystonia have been recognized [17]. Neuroimaging is useful in virtually all combined dystonias, because it can provide important diagnostic clues [20]. Metal deposition can be detected by neuroimaging on computed tomography (e.g., copper) or MRI (e.g., iron) [21]. Presynaptic dopaminergic scan (DAT or ^{18}F DOPA) is useful to differentiate between dopa-responsive dystonia and juvenile Parkinson disease presenting with dystonia [22]. This can also be useful to distinguish dystonic tremor from parkinsonian tremor [13]. In combined dystonia syndromes, laboratory testing is useful and should be targeted on the syndromic pattern. For example, dystonia combined with parkinsonism leads to a list of disorders for more targeted diagnostic testing such as DRD, Wilson disease, genetic forms of parkinsonism which often have young-onset and recessive inheritance (PARK2, 6, and 7), X-linked dystonia-parkinsonism/Lubag (DYT3), rapid-onset dystonia-parkinsonism (DYT12), and neurodegeneration with brain iron accumulation (including PANK2- and PLA2G6-associated neurodegeneration, neuroferritinopathy, and others) [21].

When a specific etiology cannot be determined, it is important to follow patients and revise the diagnosis as additional clinical fea-

tures are recognized. Many combined dystonic disorders may present first with what appears to be isolated dystonia, and additional clinical features may develop over the following months or years as in the case of parkinsonian syndromes, in which isolated limb dystonia may be the presenting feature [22]. In Parkin disease, particularly, dystonia at onset may occur in over 40% of cases [23]. It is not until other clinical features emerge that the diagnosis becomes more obvious.

Conclusions

The diagnosis of dystonia remains a difficult exercise. The new classification scheme helps in supporting the identification of dystonia syndromes in the clinical setting. A careful evaluation is needed for all patients with dystonia along axis I guidance, in order to identify uncommon subtypes where specific etiology-based treatments can dramatically alter the course of the disorder. Botulinum toxins are the treatment of choice for most focal and segmental dystonias and may be used also to target specific regions in patients with broader spread. Deep brain stimulation and other surgical procedures are available when oral medications and botulinum toxins provide inadequate relief of symptoms.

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