REVIEW ARTICLE

Dystonia: diagnosis and management

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Clinical practice in dystonia has greatly evolved in recent years; a synthetic review on patient management is provided here. Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures or both. A recent classification has innovated clinical practice and serves as guidance for clinical assessment: Axis I describes clinical features, whereas Axis II indicates etiology. Dystonia presents with different syndromic aggregations with varied somatic involvement and some common features. There are five recognizable physical signs of dystonia: two main signs (dystonic postures and movements) and three additional signs (*gestes antagonistes* or tricks, mirror dystonia and overflow dystonia). There is still no validation of diagnostic criteria for the different dystonia syndromes, and many cases with mild phenomenology remain undiagnosed. Patients with dystonia also present non-motor features that are variably combined with the movement disorder. The features of the most common inherited and acquired dystonia syndromes are reviewed here. There is clear evidence of genetic–environmental interaction in the determinism of dystonia. The diagnostic process is guided by clinical examination and based on specific laboratory examinations. Symptomatic treatments are available for dystonia: botulinum neurotoxin injections are the primary choice for most focal dystonia syndromes; deep brain stimulation is useful in some generalized and non-generalized syndromes. Additional treatment strategies are currently being assessed.

Introduction

More than 100 years have passed since Oppenheim first introduced the term dystonia [1], and more than 40 since David Marsden and Stanley Fahn first attempted to define and classify different dystonia syndromes [2,3]. Meanwhile, the phenomenology of dystonia has been described in great detail and several genetic forms have been recognized. Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures or both [4]. 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.

The hyperkinetic disorder of dystonia is not always easy to recognize, and it is often misdiagnosed [5]. Dystonia shares some features with parkinsonian states: it causes bradykinesia [6], may coexist with parkinsonism, and is observed in Parkinson's disease (PD) as an off-related phenomenon or a transition dyskinesia [7,8]. The physical signs of dystonia are easy to recognize when combined into a full-house syndromic association, but instead more difficult when mild or isolated.

Epidemiology

Attempts to assess the overall epidemiology of dystonia have led to uncertain figures because of its wide heterogeneous expression. Overall, dystonia is not a rare disease, but several inherited or idiopathic dystonia syndromes fall into the current definition of rare chronic debilitating diseases.[1] Published epidemiological studies have probably

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[1]See for example the definition of rare diseases provided by the European Commission (https://ec.europa.eu/health/rare_diseases/policy_en).

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underestimated the prevalence of dystonia in the general population when accounting for 15–30 cases per 100 000 [9,10]. A classic population study in Rochester (Minnesota) reported a similar crude prevalence rate for all focal dystonia syndromes [11]. In a study of a random sample of the population over 50 years of age, the prevalence of isolated dystonia was estimated to be 732 per 100 000, suggesting that in the aging population dystonia is a common neurological disorder [12]. The reported variability amongst epidemiological studies denotes a difficulty in ascertaining the diagnosis of dystonia, given the lack of validated criteria and the occurrence of a significant proportion of patients with mild phenomenology who do not request a medical consultation.

Women are affected about twice as often as men. Of note, although the genetic causes of dystonia – especially for adult-onset focal forms – are still largely elusive, a positive family history is reported in about 20% of dystonia sufferers [13–15]. Adult-onset focal dystonia syndromes are by far the most frequent presentations. In two recent studies on focal syndromes, the majority of patients had cervical dystonia (69%) or blepharospasm (17%) [15,16], whilst other forms were much rarer: limb dystonia (3%–7%), spasmodic dysphonia (1%–3%), musician's dystonia (3%) and oromandibular dystonia (1%).

Classification

The recent classification of dystonia has greatly innovated clinical practice and serves as a guide for clinical assessment [4].

Axis I depicts clinical features and provides a synthetic snapshot of the patient's clinical condition at the time of examination, whereas Axis II accommodates etiology (Fig. 1). Five descriptors are listed under Axis I: age at onset, body distribution, temporal pattern, co-occurrence of other movement disorders or of other neurological manifestations. Five age groups are distinguished for age at dystonia onset: infancy (birth to 2 years), childhood (3–12 years), adolescence (13–20 years), early adulthood (21–40 years) and late adulthood (>40 years). The body distribution can be focal, segmental, multifocal, generalized (with or without leg involvement) or unilateral (hemidystonia). The temporal pattern includes the disease course, which may be

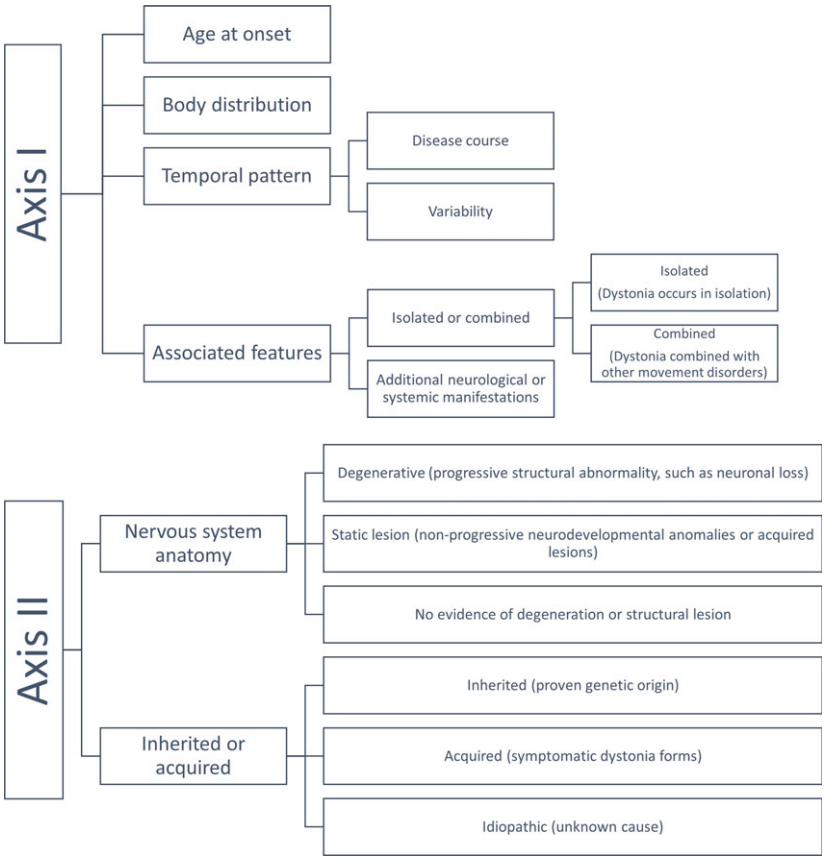

Figure 1 Hierarchical organization of Axis I (clinical characteristics) and Axis II (etiology) of the dystonia classification.

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static or progressive, and the variability of symptoms, which may be persistent, fluctuating, action specific or paroxysmal. Associated features indicate whether dystonia is combined with another movement disorder (e.g. myoclonus dystonia) or with other neurological or systemic manifestations.

If a patient's condition progresses, its description along Axis I will vary over time and the sequence of consecutive observations will describe progression. Instead, for the etiological classification (Axis II), the most recent information available will be used.

Clinical features

The motor features of dystonia were originally observed in generalized cases and later recognized to occur also in focal syndromes with cervical or limb involvement [17]. The features of dystonia encompass two main physical signs that can be recognized by expert neurological assessment (Table 1). Since the diagnosis is based on clinical observation and there are no supportive laboratory measures, the clinical recognition is easier when there is a full-house phenomenology, more difficult – instead – when dystonic movements occur in isolation. Tremor may be an isolated dystonic movement; therefore, isolated tremor syndromes may be misdiagnosed as non-dystonic tremor syndromes (see below). Additional clinical signs, such as a *geste*, may support a diagnosis of dystonia, but the clinical picture may still remain below a threshold of diagnostic confidence. People with mild focal phenomenology may have no complaint or may not consult a doctor; hence, it is not uncommon to recognize a focal dystonia in unaware or uncomplaining subjects. The diagnosis of dystonia can be delayed or missed more frequently than that of other hyperkinetic movement disorders.

The physical signs listed in Table 1 are commonly observed in patients with cervical or limb involvement. Additional signs observed in patients with blepharospasm are the presence of stereotyped, bilateral and synchronous spasms of the orbicularis oculi muscles. Spasms may be brief or sustained and may induce narrowing or closure of the eyelids, but of course have no torsional attitude [18]. In the case of laryngeal dystonia, instrumental examination can reveal spasmodic contractions of the vocal folds (abductor or adductor dysphonia), also without overt torsional appearance [19]. In muscle tension dysphonia, instead, the involuntary contractions affect the accessory phonation muscles without necessarily involving the vocal folds.

In addition to producing the positive motor phenomena listed in Table 1, dystonia may also present failure of willed activity to occur. This has been documented in blepharospasm (where the so-called 'apraxia of eyelid opening' is in fact an inability of voluntary eyelid opening) [20], upper limb dystonia [21] and cervical dystonia [22]. Finally, dystonia is associated with slowing of movement (dystonic bradykinesia) [23], to be distinguished from parkinsonian bradykinesia [24].

Dystonia is called 'isolated' when it is the sole motor feature. The observation of tremor, representing a dystonic movement, is compatible with the definition of isolated dystonia. If additional movement disorders occur, dystonia is called 'combined'. Typical combined dystonia syndromes are myoclonus dystonia or dystonia parkinsonism. When dystonia is associated with other neurological or systemic manifestations, these are annotated as associated features (Fig. 1).

Transition from old to new terminology

The recent introduction of a new classification system of dystonia [4] has occasionally raised uncertainties on how to translate the old terminology. The newly introduced definitions provide better clarity of language and meaning but are not exactly synonymous with older terms. The traditional expression 'primary' dystonia is now discouraged and can be translated as 'isolated idiopathic' or 'isolated inherited' dystonia. 'Pure' dystonia is an obsolete denomination for isolated dystonia. 'Dystonia plus' and 'heredodegenerative dystonia' can be translated, respectively, to 'combined dystonia' or 'dystonia associated with neurological/systemic manifestations'. The newer expressions are sometimes longer; still, they hold the advantage of conveying more detailed information than older terms.

Non-motor features of dystonia

Recent studies have revealed that, in addition to the movement disorder, there are other, non-motor, features in patients with isolated dystonia.

Sensory abnormalities may present months before the movement disorder develops, as mild neck discomfort preceding cervical dystonia, irritation or dry eyes before the development of blepharospasm, or throat irritation heralding the onset of spasmodic dysphonia [25]. Pain is reported in nearly 70% of patients with cervical dystonia and in up to 30% of those with focal hand dystonia or writer's cramp [26].

Dystonia is also associated with neuropsychiatric abnormalities, such as depressive disorders, that are more frequent in cervical dystonia, blepharospasm, laryngeal dystonia and focal hand dystonia compared to healthy controls. A family history of depression, anxiety and social anxiety is more common in

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Table 1 The five physical signs of dystonia syndromes are recognized in most patients with dystonia

Physical sign	Description
Main physical signs	
Dystonic postures	Muscle contractions may be continuous, forcing limbs and trunk into sustained postures (not available for blepharospasm or laryngeal dystonia) • A body part is flexed or twisted along its longitudinal axis • Slowness and clumsiness for skilled movements is associated with sensation of rigidity and traction in the affected part
Dystonic movements	These features have to be looked for in all movement disorders, either fast or slow, also when the immediate impression is that of a tremor, tic, chorea or myoclonus • Tremor is a feature of dystonic movements and may appear as isolated tremor • Movements are repetitive and patterned (i.e. consistent and predictable) or twisting • Movements are often sustained at their peak to lessen gradually in a preferred posture (usually opposite to the direction of movement)
Additional physical signs	
Gestes antagonistes ('tricks')	Voluntary actions performed by patients that reduce or abolish the abnormal posture or the dystonic movements. They are usually simple movements involving, or directed to, the body region affected by dystonia • These movements are natural and graceful, not consisting of forceful opposition to the phenomenology of dystonia • The movement does not push or pull the affected body part but simply touches it ('sensory trick') or accompanies it during alleviation of dystonia • Alleviation of dystonia occurs during the *geste* movement, usually soon after its start Alleviation may last for as long as the *geste* or slowly reverses spontaneously before its end To be distinguished from *geste*-like voluntary movements
Mirror dystonia	It is evaluated in the upper or lower limbs. At least three different types of repetitive tasks (e.g. finger sequence, normal writing or piano-like movements) are performed at low and fast speed in the non-affected limb It is a unilateral posture or movement with the same or similar characteristics to the patient's dystonia (usually postures and some movements) that can be elicited, usually in the more severely affected side, when contralateral movements or actions are performed To be distinguished from non-dystonic mirror movements
Overflow dystonia	It is observed at least once, usually ipsilaterally, in coincidence with the peak of dystonic movements It is an unintentional muscle contraction accompanying the most prominent dystonic movement that are observed in an anatomically distinct neighboring body region

Dystonic postures are not observed in patients with blepharospasm; mirror dystonia is only observed when the limbs are affected. Modified from [69].

dystonia than in controls [27]. Some specific inherited dystonia syndromes have clear association with non-motor features, as observed, for example, in aggregated cohorts of patients with DYT11 dystonia [28].

In isolated dystonia syndromes, whether idiopathic or inherited, there are usually no cognitive abnormalities; by contrast, cognitive abnormalities are often found in combined (whether inherited or idiopathic) syndromes (Table 2).

Etiology

Classification by etiology is listed under Axis II. This is an evolving area, particularly concerning genetic discoveries.

Evidence of degeneration, at the macroscopic, microscopic or imaging level, provides a useful tool to identify degenerative dystonias. Degeneration is defined as a progressive structural abnormality, such as neuronal loss, related to the occurrence of dystonia. Static lesions are non-progressive neurodevelopmental anomalies or acquired lesions. Incidental findings, unrelated to the observed dystonia phenotype, are not taken into account. In cases of isolated dystonia, usually there is no evidence of either degeneration or structural lesion under Axis II.

Axis II specifies whether dystonia is acquired (due to a known specific cause), inherited (due to a pathogenic genetic mutation) or idiopathic (possibly related to a yet undiscovered genetic defect).

Inherited dystonia syndromes

The number of inherited syndromes is continuously increasing. They can present with isolated dystonia or with a combination of dystonia plus another movement disorder (Table 2). Some common syndromic associations are highlighted hereafter.

Isolated dystonia

Dystonia is the only disease manifestation with the possible occurrence of tremor. The best characterized form is DYT1 dystonia, also called DYT-TOR1A

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Table 2 Common inherited dystonia syndromes, grouped according to Axis I criteria

Progressive listing (gene/protein)	Proposed name [29]	Inheritance	Phenomenology
Inherited isolated dystonia syndromes			
DYT1 (*TOR1A*/torsinA)	DYT-TOR1A	AD	Early-onset generalized dystonia. Typically, there is limb onset and sparing of face and neck. Alternative phenotypes have been described
DYT4 (*TUBB4*/tubulin beta 4A class IVa)	DYT-TUBB4A	AD	Rare form of dystonia presenting more commonly with spasmodic dysphonia, with craniocervical involvement and possible later generalization
DYT6 (*THAP1*/THAP domain containing apoptosis-associated protein 1)	DYT-THAP1	AD	Adolescent or young adult onset, generalized or segmental involvement with predominance of craniocervical and laryngeal features
DYT24 (*ANO3*/anoctamin 3)	DYT-ANO3	AD	Adult-onset tremulous craniocervical dystonia with laryngeal involvement and upper limb tremor
DYT25 (*GNAL*/guanine nucleotide-binding protein subunit alpha L)	DYT-GNAL	AD	Adult-onset focal craniocervical dystonia, typically progressing to involve larynx, trunk and limbs
Inherited combined syndromes			
DYT5a (*GCH1*/GTP cyclohydrolase 1)	DYT/PARK-CGH1	AD	Childhood- or young adult-onset dopa-responsive dystonia with parkinsonism and diurnal fluctuations
DYT5b (*TH*/tyrosine hydroxylase)	DYT/PARK-TH	AR	Milder form of dopa-responsive dystonia with infantile or early childhood onset
DYT3 (*TAF1*/TATA box-binding protein-associated factor 1)	DYT/PARK-TAF1	XD	Segmental or generalized dystonia with marked oromandibular involvement and parkinsonism unresponsive to levodopa. Endemic in Panay, Philippines, where it is known as Lubag
DYT12 (*ATP1A3*/ATPase Na^+/K^+ transporting subunit alpha 3)	DYT/PARK-ATP1A3	AD	Different phenotypes, including bridging forms, have been described: rapid-onset dystonia parkinsonism, alternating hemiplegia of childhood and CAPOS syndrome
PARK2 (*parkin*/E3 ubiquitin ligase)	PARK-Parkin	AR	Young-onset parkinsonian syndrome with sustained response to dopaminergic treatment and prominent leg dystonia
DYT11 (*SGCE*/epsilon-sarcoglycan)	DYT-SGCE	AD	Myoclonus dystonia with predominant neck and upper limb involvement
N/A (*NKX2*.1/homeobox protein Nkx-2.1)	CHOR-NKX2-1	AD	Onset with chorea which can be replaced by a myoclonus dystonia phenotype during the disease course
N/A (*ADCY5*/adenylate cyclase 5)	CHOR-DYT-ADCY5	AD	Varied phenotype, including childhood-onset paroxysmal or persistent chorea and dystonia
DYT10 (*PRRT2*/proline-rich transmembrane protein 2)	PxMD-PRRT2	AD	Paroxysmal dystonia and choreoathetosis
DYT8 (*MR1*/myofibrillogenesis regulator 1)	PxMD-PNKD	AD	Attacks of paroxysmal non-kinesigenic dystonia, chorea, athetosis or ballismus precipitated by specific factors such as alcohol, caffeine, stress, hunger, fatigue or tobacco
DYT18 (*SLC2A1*/glucose transporter protein type 1)	PxMD-SLC2A1	AD	Paroxysmal exertion-induced chorea and dystonia in excessively exercised body regions
Inherited combined syndromes associated with additional neurological abnormalities			
SCA3 (*ATXN3*/ataxin-3)	SCA-ATXN3	AD	Ataxic syndrome that may present with parkinsonism, dystonia, chorea, spasticity, neuropathy or lower motor neuron involvement
SCA17 (*TBP*/TATA box binding protein)	SCA-TBP	AD	Ataxic syndrome that may present chorea and dystonia; it may be associated with dementia and psychosis
N/A (*TIMM8A*/mitochondrial import inner membrane translocase subunit Tim8 A)	DYT-TIMM8A	XD	Mohr–Tranebjaerg syndrome: dystonia plus additional clinical features such as sensorineural deafness, visual or cognitive impairment, behavioral problems, pyramidal signs
N/A (*DCAF17*/nuclear transmembrane protein)	NBIA/DYT-DCAF17	AR	Woodhouse–Sakati syndrome: dystonia and additional clinical features such as dysarthria, deafness, seizures, cognitive impairment, hypogonadism, alopecia, diabetes mellitus, thyroid dysfunction

(continued)

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Table 2 *(Continued)*

Progressive listing (gene/protein)	Proposed name [29]	Inheritance	Phenomenology
NBIA1 or PKAN (*PANK2*/pantothenate kinase 2)	NBIA/DYT-PANK2	AR	Dystonia with onset in childhood or adolescence, combined dysarthria, rigidity, pyramidal signs and cognitive impairment (previously called Hallervorden–Spatz disease)
NBIA2, PARK14 or PLAN (*PLA2G6*/A2 phospholipase)	NBIA/DYT/PARK-PLA2G6	AR	Dystonia often combined with chorea, parkinsonism, dementia, pyramidal signs and psychiatric features

This listing is not exhaustive. AD, autosomal dominant; AR, autosomal recessive; XD, X-linked dominant; N/A, not available.

[29]. DYT1 dystonia is caused by mutations in the *TOR1A* gene, encoding torsinA, a member of the ATPases family. Almost all cases are caused by a specific mutation, a 3-base pair deletion (delGAG) in the coding region. This is the prototype of inherited isolated generalized dystonia with limb onset, and it is believed that Oppenheim's original description included patients with this inherited form [30]. Symptoms usually start in childhood with lower limb dystonia and later spread to generalization. The face and neck are typically not involved, a useful clue for clinical orientation.

By contrast, there are inherited isolated syndromes with a prominent craniocervical onset. DYT6 dystonia (DYT-THAP1) may remain segmental or generalized, and often has a striking laryngeal involvement. DYT25 dystonia (DYT-GNAL) also causes adult-onset cervical or cranial dystonia, often with prominent tremor. Other generalized syndromes are still debated and not yet confirmed, such as DYT4 (DYT-TUBB4A), a rare generalized dystonia often with laryngeal onset and cranial–cervical involvement, and DYT23 dystonia (DYT-CIZ1), associated with adult-onset autosomal dominant cervical dystonia and tremor.

DYT24 (DYT-ANO3) is a cervical isolated dystonia syndrome due to mutations of the *ANO3* gene that encodes a transmembrane protein belonging to a family of calcium-activated chloride channels. Dystonic tremor has been described as a key feature of DYT24 dystonia, appearing most commonly as head or arm tremor, and may precede the appearance of dystonic postures. Generalization has been described in approximately 10% of cases [31].

Isolated dystonia may be the presenting feature of combined syndromes that can remain isolated for a significant amount of time before another movement disorder appears. An isolated dystonia may be the long-standing presenting feature of PARK2 parkinsonism (PARK-Parkin) [32], of rapid-onset dystonia parkinsonism (DYT12, DYT-ATP1A3) [33], of Lubag disease (DYT3, DYT/PARK-TAF1) [34] and of dopa-responsive dystonia (DYT5a, DYT-GCH1 [35] or DYT5b, DYT-TH [36]). In most cases, a full-house syndrome of combined dystonia will develop in time, whilst in some cases the phenotype will remain limited to isolated dystonia.

Dystonia combined with myoclonus

The term 'myoclonus dystonia' is used to indicate the occurrence of true myoclonus (particularly as "lightning jerks") in combination with typical features of dystonia in patients without evidence of degeneration or structural lesion; this sets a difference with 'myoclonic' dystonia, a rather old term referring to cases of isolated dystonia where very fast and brief dystonic movement has a myoclonus-like appearance. Action-induced, alcohol-responsive myoclonic jerks of subcortical origin are typically combined with dystonia in DYT11 myoclonus dystonia (DYT-SGCE). The myoclonic jerks typically are brief, lightning-like and often affecting prevalently the neck, the trunk and the upper limbs. Dystonia occurs in about two-thirds of patients, usually in the form of mild cervical dystonia and writer's cramp. Some patients with myoclonus dystonia carry no *SGCE* gene mutations and may have other gene defects (e.g. *ANO3*, *GCH1*, *TH*, *CACNA1B*, *TITF1*, *TOR1A*), with few cases remaining genetically unidentified [37].

Dystonia combined with parkinsonism

In cases with childhood onset, dystonia dominates and may be the only motor sign, whereas parkinsonism becomes more prominent with increasing age. Several forms have a disorder of dopamine metabolism, diurnal fluctuation of symptoms and a sustained response to levodopa. Dopa-responsive dystonia (DRD) syndromes include autosomal dominant DYT5a (DYT/PARK-GCH1) and autosomal recessive syndromes with more severe phenotypes, such as DYT5b (DYT/PARK-TH) or sepiapterin reductase deficiency (DYT/PARK-SPR).

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In some patients, parkinsonism dominates; in others dystonia prevails, particularly in the legs. The differential diagnosis is with inherited juvenile PD, particularly autosomal recessive parkinsonisms, such as PARK2 (PARK-Parkin), PARK7 (PARK-DJ1) or PARK6 (PARK-PINK1). In the latter cases, both dystonia and parkinsonism improve with dopaminergic medication [32].

In addition, there are combined dystonia parkinsonism syndromes that are partially responsive to levodopa, such as rapid-onset dystonia parkinsonism (DYT12, DYT-ATP1A3), DYT3 (DYT-TAF1, Lubag disease) and DYT16 (DYT-PRKRA) (Table 2).

Dystonia combined with ataxia

Several autosomal dominant spinocerebellar ataxias (SCAs) can have dystonia as a part of the phenotype and occasionally as the presenting feature. Dystonia is most commonly observed in SCA1, SCA2, SCA3, SCA6 and SCA17 [38,39].

Acquired dystonia syndromes

It is remarkable that dystonia syndromes indistinguishable from idiopathic may be caused by discrete brain lesions [40]. Lesions causing acquired dystonia are prevalently located in the basal ganglia, thalamus, corticospinal tract or cerebellum and have a varied etiology (Table 3). Frequent etiologies include vascular or traumatic lesions, perinatal brain injury and neuroleptic usage.

Table 3 Main categories of acquired dystonia syndromes

Pathophysiology	Etiology
Dystonic cerebral palsy	Perinatal brain injury
Drug-induced	Neuroleptics, dopamine blockers, anticonvulsants, calcium channel blockers
Toxic	Heroin inhalation, methanol, carbon monoxide, disulfiram, cyanide, manganese, cobalt, 3-nitropropionic acid
Brain lesion	Ischaemic, hemorrhagic, arteriovenous malformation, neoplasms, radiotherapy, head trauma, brain surgery (including ablations and stereotactic lesions), electrical injury
Infection	Viral encephalitis, subacute sclerosing panencephalitis, human immunodeficiency virus, encephalitis lethargica, prion disease
Immune-mediated	Acquired disseminated encephalomyelitis (ADEM), autoimmune or paraneoplastic encephalitis (most frequently NMDAR antibody-associated encephalitis)
Metabolic	Hypoglycemia, hyperglycemic hyperosmolar state, hypocalcemia, hypoparathyroidism, hyperthyroidism, hepato-cerebral degeneration, uremia

Common phenotypes of acquired dystonia encompass hemidystonia, which is caused by static brain lesions in the contralateral hemisphere; Vogt's 'double athetosis' caused by cerebral palsy; and axial dystonia caused by neuroleptics. By contrast, cervical dystonia is most often idiopathic or inherited, although it has been occasionally described also in acquired cases [41]. There is no altogether reliable clinical clue to distinguish acquired from non-acquired dystonia syndromes.

Genetic–environmental interplay

Dystonia syndromes are evidently influenced by both genetic and environmental factors. This interaction is particularly evident in isolated dystonia. An epidemiological study performed in Australia showed that anxiety disorders, tremor, cigarette smoking and head injuries with a loss of consciousness were associated with increased risk of idiopathic isolated dystonia [42]. The first two factors may be either causative or secondary to dystonia, whereas the last two are probably contributing environmental variables. Similar results have been found in focal dystonia syndromes. Not surprisingly, spasmodic dysphonia is associated with several endogenous and exogenous factors [43], and musician's dystonia is probably caused by skilled perfectionist training in genetically predisposed individuals [13]. It has also been shown that environmental factors may facilitate or worsen different focal dystonia syndromes, such as exposure to bright light for blepharospasm [44] or repeated skilled exercise for task-specific dystonia [45]. Differences in prevalence, age of onset and gender are probably correlated with different exposures to environmental factors on a background of genetic susceptibility.

Environmental factors play a role also in inherited dystonia syndromes. A first evidence is provided by the observation of incomplete penetrance: in DYT-TOR1A penetrance is quite low, around 30%–40% [46], whereas in DYT-THAP1 it is about 60% [47]. This suggests that yet unknown environmental and lifestyle factors can influence the expression of pathogenic mutations even in early-onset dystonia syndromes.

Diagnosis

The phenomenology of dystonia is a collection of physical signs, including tremor, that require expert neurological assessment [48,49]. The first diagnostic criteria were proposed by Herz [50], who recognized that dystonic movements and postures are the hallmark phenomenology of dystonia. They constitute the

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main physical signs and are complemented by three other physical signs: *gestes antagonistes* ('tricks'), mirror dystonia and overflow dystonia. Fahn first noticed that dystonic movements are the most common type of involuntary movements to be misdiagnosed [51], are highly variable (either fast or slow, and irregular) and may manifest as isolated tremor without other clues suggesting dystonia. This may delay recognition of dystonia in patients with an isolated tremor syndrome [48]. The minimal requirements for diagnosing dystonia in specific body regions are still for the most part undefined and, whilst the full-house phenomenology remains unquestionable, mild or incomplete expressions, in the past called *formes frustes* [52], may remain undiagnosed.

There is no consensus on diagnostic criteria for focal dystonia syndromes; therefore, only general diagnostic criteria are currently available. A set of proposed diagnostic criteria for blepharospasm [53] still needs validation and refinement; a concerted effort for consensus on diagnostic criteria for cervical dystonia is currently under way.

Tremor in dystonia

Traditionally, tremor was considered a separate movement disorder from dystonia, although the recent consensus classification has ratified that dystonic movements can present as isolated tremor [4]. In patients with dystonia, tremor commonly involves the head or the arms, where it can be postural/kinetic or at rest [54]. Head tremor is quite specific of dystonia, but isolated arm tremor can be mistaken for essential or parkinsonian tremor [48].

Upper limb tremor is observed in a significant proportion of patients with otherwise isolated focal dystonia syndromes, such as cervical dystonia, focal upper limb dystonia or spasmodic dysphonia [15]. It is accepted that patients with dystonia may have a classic essential tremor phenomenology and later may develop dystonic postures to compose a full-house clinical picture. It is not uncommon that patients with isolated upper limb postural/kinetic tremor are misclassified as having classic essential tremor if upper limb tremor is the presenting sign and the patients are observed before they develop any other signs of dystonia. The expression 'isolated upper limb tremor' is increasingly used to describe patients who cannot be definitely classified as having essential or instead dystonic tremor.

Patients with adult-onset dystonic tremor can also be misdiagnosed as having PD, particularly if they have upper limb dystonic resting tremor and are not assessed by dopaminergic imaging. Large clinical trials on PD have shown that a percentage between 10% and 15% of clinically diagnosed PD patients have normal dopaminergic binding (scans without evidence of dopaminergic deficit) [55,56]. Some of these patients have adult-onset isolated dystonia [57] that is particularly difficult to recognize when dystonic bradykinesia causes reduced arm swing while walking [58].

Investigations

The diagnosis of dystonia is primarily clinical, and investigations are needed particularly for Axis II classification. After outlining a syndromic description according to Axis I, syndrome-specific investigations are performed to establish an etiological diagnosis according to Axis II (Fig. 2). In some cases, clinical examination may prompt specific investigations. For example, the observation of a Kayser–Fleischer ring may lead to a study of copper metabolism or the observation of myoclonus dystonia may warrant specific genetic testing.

Electromyography (EMG) mapping may provide a complement to clinical examination, allowing some typical neurophysiological phenomenology to be recognized. The usual EMG features observed in dystonia are as follows: prolonged bursts (200–500 ms), simultaneous contractions (cocontraction) of agonist and antagonist muscles, involuntary activation of contiguous muscles (overflow) [59].

Most patients will undergo an imaging study, usually starting with brain magnetic resonance imaging (MRI), to identify whether there is a degenerative condition, a static lesion or no evidence of brain lesions. Results of imaging studies may prompt further investigations. For example, a suspicion of neurodegeneration with brain iron accumulation or a cerebellar atrophy may lead to specific genetic testing. In dystonia parkinsonism syndromes, by contrast, brain imaging may be abnormal and shows accumulation of metals: manganese, as in Kufor–Rakeb syndrome (PARK-ATP13A2) [60]; calcium, as in primary familial brain calcifications [61]; iron, as in neurodegenerations with brain iron accumulation [62]. A brain computed tomography scan is preferable if calcifications are suspected; otherwise MRI is the neuroimaging of choice. As a rule, brain MRI should include iron-sensitive sequences [63].

In patients where the workup has ruled out evidence for an acquired or inherited dystonia syndrome, a provisional diagnosis of idiopathic dystonia is made. The high degree of phenotypic overlap has facilitated the diffusion of multi-gene diagnostic dystonia panels [64].

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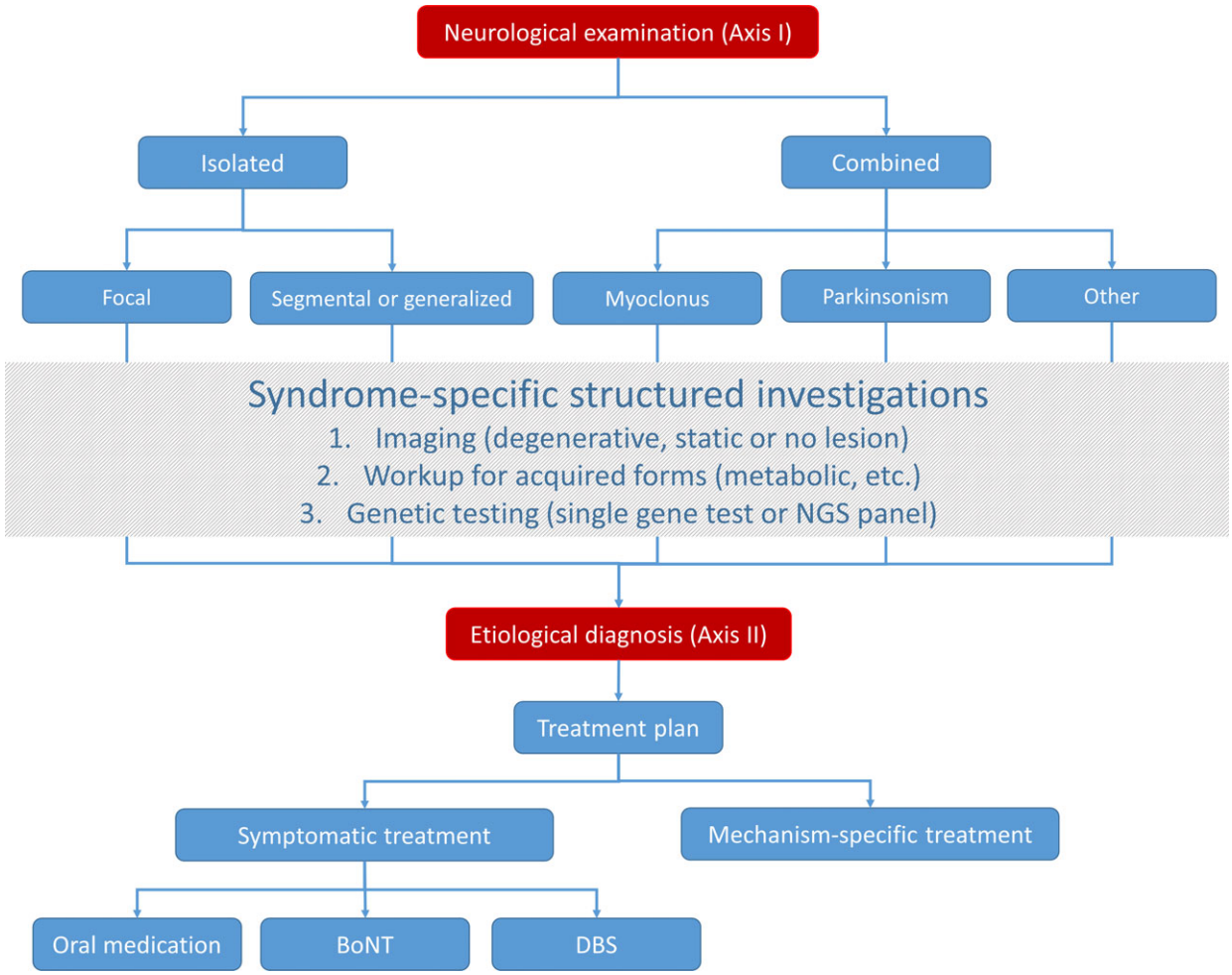

Figure 2 Clinical strategy from examination to treatment plan. Following examination, phenomenology guides diagnostic testing. The information collected allows a treatment plan, whether symptomatic or mechanism specific, to be defined. A listing of specific disease-modifying treatments for dystonia syndromes has recently been compiled [94]. BoNT, botulinum neurotoxin; DBS, deep brain stimulation; NGS, next-generation sequencing. [Colour figure can be viewed at wileyonlinelibrary.com]

Metabolic and blood testing (e.g. acanthocytes, ceruloplasmin, serum and urinary copper, uric acid, serum pyruvate, and lactate levels) and other complementary investigations (e.g. slit-lamp examination) are usually performed in specific cases to reach a diagnostic confirmation. DAT scan scintigraphy allows reduced binding to dopaminergic terminals to be identified, indicating a parkinsonian syndrome.

Treatment/management

Anticholinergic medications have proved useful in patients with generalized and focal isolated dystonia syndromes, whereas levodopa is effective in some patients with dopa-responsive dystonia parkinsonism. Other agents that have been used in dystonia are baclofen, carbamazepine and benzodiazepines, either alone or in combination [65].

Botulinum toxin treatment

Botulinum neurotoxin (BoNT) is a potent poison produced by *Clostridium botulinum* that causes local muscle weakness. Its efficacy is due to partial peripheral denervation [66] with a contribution of central effects [67].

Botulinum neurotoxin is the first-line treatment for patients with blepharospasm and cervical dystonia (spasmodic torticollis) [68]. It is also effective in laryngeal and limb dystonia. Three BoNT/A serotypes and one BoNT/B serotype are commercially available worldwide. They have received individual generic names and are currently considered individual products that are only partly interchangeable [69]. In addition, other BoNT products are available in specific countries and others are under development [70].

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Cervical dystonia

There is class A evidence of efficacy for Abo BoNT/A and Rima BoNT/B and class B evidence for Ona BoNT/A and Inco BoNT/A in cervical dystonia [71]. BoNT/A products are commonly used as first-line therapy for cervical dystonia.

The efficacy of BoNT products in cervical dystonia has been confirmed by several systematic reviews. BoNT/A is more effective than placebo [72] and anticholinergic oral treatment [73]. BoNT/B has also proven efficacious in cervical dystonia [74]; a comparison of BoNT/A and BoNT/B showed significant improvement from baseline without difference between the median duration of benefit [75].

There is no standard procedure for performing BoNT injections in cervical dystonia: muscle selection, BoNT dilution and dosing, and targeting techniques (whether to use EMG or ultrasound guidance) vary significantly amongst centers, which probably brings some heterogeneity in outcome. Two recent consensus publications have provided a first attempt to develop practice guidelines for BoNT treatment in cervical dystonia [76,77].

Blepharospasm

There is class B evidence on the efficacy of Ona BoNT/A and Inco BoNT/A and class C evidence for Abo BoNT/A in blepharospasm [71]. BoNT/A is the first-line treatment in this condition, with an expected success rate approaching 100% if injections are placed in the pretarsal portion of the orbicularis oculis muscle [78,79].

Other focal dystonias

Botulinum neurotoxin type A is probably effective for the treatment of focal upper limb dystonia (including writer's cramp) and adductor spasmodic dysphonia (adductor laryngeal dystonia) [80], whilst abductor laryngeal dystonia responds less predictably [68]. Notwithstanding, BoNT/A is the treatment of choice also for these conditions given the lack of alternative treatments.

Most patients with dystonia have a long-term response to BoNT after repeated treatment cycles [81]. However, in some patients the efficacy of BoNT treatment may lessen to the extent that a patient may be considered to have lost a tangible benefit. This condition, called 'secondary non-response', is caused almost always by wrong muscle targeting, possibly due to changes in the muscle activation pattern over time. The development of neutralizing antibodies is a theoretical possibility that is considered exceptional: after long-term treatment with ona BoNT/A, only <2% of the patients were positive for neutralizing antibodies [82].

Transcranial magnetic stimulation

Repetitive, low frequency transcranial magnetic stimulation can enhance intracortical inhibition, a neural process deemed to be altered in dystonia. Although single-session studies have been reported to be ineffective, there is preliminary evidence that cumulative effects can be obtained by repeated stimulation over consecutive days [83].

Deep brain stimulation

Deep brain stimulation (DBS) of the internal globus pallidus (GPi) has emerged as the surgical treatment of choice for children and adults with disabling idiopathic isolated dystonia. The efficacy of DBS has been well documented in patients with inherited generalized dystonia, particularly DYT1 dystonia which cannot be managed with oral medications or BoNT. This therapeutic approach has been extended more recently to focal dystonia syndromes, which are commonly treated with BoNT.

Evidence of the efficacy of bilateral DBS of the GPi on DYT1 dystonia is confirmed by several studies [84,85]. Compared to patients with idiopathic (not inherited) isolated dystonia, DYT1 patients had earlier and greater improvement [86]. The efficacy of GPi DBS on other inherited isolated dystonia syndromes is less consistent than observed in DYT1. Patients with DYT6 dystonia respond less favorably to GPi DBS than DYT1 mutation carriers [86,87]. There is insufficient evidence of the efficacy of GPi DBS on patients with DYT24 tremulous-prominent cervical dystonia [31], although it is generally believed that dystonic tremor responds to GPi DBS implants [88].

The efficacy of GPi DBS has been consistently reported in DYT11 (DYT-SGCE) myoclonus dystonia and in DYT3 (DYT/PARK-TAF1 or Lubag) X-linked dystonia parkinsonism. In DYT11, both dystonia and myoclonus improve and a sustained benefit has been reported after 10 years [89]; in Lubag, instead, dystonia can improve more than parkinsonism but long-term assessments are lacking [90]. In other inherited combined syndromes, however, there is no clear indication of DBS efficacy. In DYT12 dystonia, instead, there is evidence of inefficacy for GPi DBS [33].

Globus pallidus internus DBS has also proved efficacious in acquired dystonia syndromes. The response of drug-induced, tardive, dystonia may be very rapid and occurs within days or weeks after bilateral GPi implants. In most cases, patients with generalized or segmental tardive dystonia have been

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treated. The available data are mainly uncontrolled case reports, and prospective systematic studies are needed instead. Dystonic cerebral palsy without prominent spasticity has also been shown to respond to GPi DBS. Most data collected are retrospective series or case reports that indicate a significant potential efficacy for DBS and call attention to the need for properly designed prospective controlled trials [91].

The subthalamic nucleus (STN) has recently been proposed as a potential DBS target, alternative to GPi in patients with dystonia. A 3-year follow-up study provided class IV evidence that STN DBS decreases long-term severity in patients with medically refractory isolated dystonia [92].

Overall, the available data suggest that DBS has great potential for different dystonia syndromes, whether idiopathic or inherited, isolated or combined. The outcome is influenced by a number of Axis I features, such as body distribution, age of onset, and by the relative prevalence of dystonic movements or postures. The genetic status is also important, with two extremes represented by DYT1 dystonia (consistently excellent outcome) and DYT12 dystonia (consistent lack of efficacy).

Physical treatments

A variety of physical treatments have been proposed for dystonia, including motor learning exercises, passive or active mobilization techniques, stretching of dystonic muscles, relaxation and electrotherapy (e.g. EMG biofeedback or transcutaneous electrical nerve stimulation). Different rehabilitation strategies have been combined with BoNT to improve disability and pain compared to BoNT treatment alone. This is still a debated topic that has particularly regarded patients with cervical dystonia and has not yet reached a consensus level [93].

Disclosure of conflict of interest

The authors declare no financial or other conflict of interests.

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