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Dystonia: clinical approach

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Abstract

Dystonia refers to sustained and vigorous contractions forcing a body region into an abnormal position that is consistently present. Dystonic postures and movements can variably combine to produce a wide spectrum of clinical presentations. The movement can affect one, two or more body regions, as in focal, segmental or generalized dystonia. Dystonic movements display specific features that can be recognised by clinical observation, such as speed, consistency, predictability, variability and relationship with voluntary movement. Sensory tricks and *gestes antagonistes* are manoeuvres that specifically alleviate dystonic movements and postures, thereby providing diagnostic clues. The diagnosis of primary dystonia can be established by applying a simple diagnostic flow chart during neurological examination to guide further laboratory testing.

Keywords: Dystonia; Primary dystonia; Diagnostic algorithm; Clinical features

1. Introduction

Dystonia is characterized by sustained muscle contractions, frequently causing repetitive twisting movements or abnormal postures [1,2]. Although dystonia is thought to be rare, it is possibly underdiagnosed or misdiagnosed due to the lack of specific clinical criteria. The classification of dystonia is based on three axes: (a) etiology, (b) age at onset of symptoms, and (c) distribution of affected body regions (Table 1). The etiological axis discriminates primary (idiopathic) dystonia, in which dystonia is the only clinical sign without any identifiable exogenous cause or other inherited or degenerative disease, from non-primary forms in which dystonia is usually just one of several clinical signs. Dystonia-plus is characterized by dystonia in combination with other movement disorders such as myoclonus or parkinsonism. Primary dystonia and dystonia-plus, whether sporadic or familial, are thought to be of genetic origin in most cases. In addition, dystonia can coexist with other clinical features (heredodegenerative diseases with dystonia), can be secondary to specific causes or may have a paroxysmal appearance (Table 1). Primary dystonias and dystonia-plus syndromes are the most important and common forms.

The prevalence of dystonia is difficult to ascertain. On the basis of the best available estimates, the prevalence of primary dystonia may be 11.1 per 100,000 for early-onset cases in Ashkenazi Jews from the 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 [3]. Primary dystonia and dystonia-plus are chronic and often disabling conditions with a broad clinical spectrum mainly in young people. Areas of specific concern include differential diagnosis with other movement disorders, etiological diagnosis, drug treatment, surgical interventions, and genetic counseling.

A task force appointed by the European Federation of Neurological Societies (EFNS) and by the European Section of the Movement Disorders Society (MDS-ES) performed a systematic review on the diagnosis and treatment of primary (idiopathic) dystonia and dystonia-plus syndromes [4]. Literature search on the diagnosis of dystonia identified no existing guidelines or systematic reviews, two consensus agreements [1,5], two reports of workshops or taskforces [6,7], 69 primary studies on clinically based diagnosis, and 292 primary studies on the diagnostic accuracy of different laboratory tests.

2. Clinical features of primary dystonia

The clinical features of dystonia encompass a combination of dystonic movements and postures to create a sustained postural twisting ("mobile" dystonia). Dystonic postures can precede the occurrence of dystonic movements and in rare cases can persist without the appearance of

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Table 1
Classification of dystonia based on three axes[a]

By cause (etiology)

- Primary (or idiopathic): dystonia is the only clinical sign and there is no identifiable exogenous cause or other inherited or degenerative disease. Example: DYT-1 dystonia.
- Dystonia-plus: dystonia is a prominent sign, but is associated with another movement disorder. There is no evidence of neurodegeneration. Example: Myoclonus-dystonia (DYT-11).
- Heredodegenerative: dystonia is a prominent sign, among other neurological features, of a heredodegenerative disorder. Example: Wilson's 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 tumor, "off"-period dystonia in Parkinson's disease.
- 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; DYT-9) 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; DYT-8) by alcohol, coffee, tea, etc. A complex familial form with PNKD and spasticity (DYT-10) has also been described.

By age at onset

- Early onset (variably defined as $\leqslant$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 localized 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)
- Generalized: 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)

[a] From Albanese et al., 2006 [4].

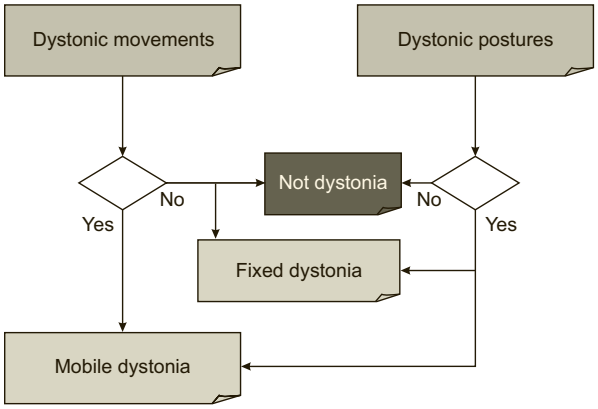

Fig. 1. Dystonia can be mobile or fixed based on the combination of postures and movements.

dystonic movements (called "fixed" dystonia; Figure 1) [8]. Sustained dystonic postures may be the presenting feature of torsion dystonia and may remain the only sign for many years before torsional movements become apparent. Dystonia has some specific features that can be recognized by clinical examination. Speed of contraction in dystonic movements may be slow or rapid, but at the peak of movement the contraction is sustained. The involuntary movement associated with dystonia is often variable over months or years and from one subject to the other. However, during a given period of observation, and within each affected individual, dystonia is distinctively consistent and predictable.

2.1. Basic features

Dystonic postures flex or twist a body part along its main axis, and are associated with a sensation of rigidity and traction. This is easy to observe on elongated body parts, such as the limbs or the trunk, but it is obviously less apparent in the cranial district. Postures are directional and force the involved body region into an abnormal position that is consistently present. In axial dystonia postural abnormalities are often a prominent feature, due to the rare occurrence of dystonic movements in the trunk. Predominantly postural forms of axial dystonia include scoliosis and camptocormia. Usually, pain is not a prominent feature of dystonia, except for cervical dystonia [9] and some secondary forms. Dystonic postures, rather than movements, may cause pain.

As a rule, dystonic movements have a twisting nature and a directional quality, are repetitive and patterned, consistent and predictable, and are sustained at their peak. The directional quality is sustained (if only for an instant), and consistency and predictability indicate that the same muscle groups are repeatedly involved. Movements are directional with variable speed. Dystonic neck movements have a directional preponderance, forcing the head to assume an abnormal position (e.g., horizontal rotation or lateral tilt), if only for a moment. Similarly, other focal forms of dystonia result in consistent directional or posturizing movements (e.g., ulnar deviation, plantar flexion, vocal cord adduction, eye closure).

Dystonic movements are occasionally rhythmic but most often arrhythmic. When rhythmic, they can be hard to differentiate from non-dystonic essential tremor [10]. Aside from their directional character, other clinical features that indicate rhythmic dystonia rather than essential tremor include: irregularity, the appearance or worsening of tremor when the affected body part is placed in a position opposite to the direction of pull, and activation of muscles not required for maintenance of the movement (overflow, as described below). By contrast, dystonic movements are easily distinguished from chorea: in dystonia there is no flowing of movement along the affected body parts, and muscle tone is not reduced. Dystonic movements may

have different speeds. When fast, they may resemble myoclonus and generate what has been termed "myoclonic dystonia" [11–13]; when slow and distal they match the description of athetosis [14]. Unlike tics, which usually change their pattern over time, dystonic movements are predictable and consistent during an observational period. Furthermore, there is no strong urge to execute the involuntary movement and no relief after execution; these are aspects of tics, which make them assume a "semi-voluntary" or at least intentional nature and are not usually observed in dystonia. In people with excessive blinking it may be difficult to distinguish the features of dystonic movements from those of motor tics. The expression "dystonic tics" has been used to indicate motor eye tics, which look like mild dystonia [15].

Dystonia is not a static phenomenon. Changes in the pattern of muscle activation occur during the course of the disease [16] and also following specific maneuvers that have a relevant diagnostic value, as reported below.

2.2. Eliciting or worsening dystonia

Overflow is observed when dystonia extends to a contiguous body region where it is not observed as an independent phenomenon. An example is overflow to the upper limb in patients with cervical dystonia. Mirroring occurs when, during a voluntary task involving a limb, similar albeit involuntary movements (often with dystonic features) arise in the contralateral limb. Mirroring is not a specific feature of dystonia, although it may reveal a latent dystonia, particularly in subjects belonging to dystonia families. When it occurs in dystonic patients, mirroring can be considered as a minimal expression of focal dystonia that is observed in otherwise unaffected body regions.

The term "action dystonia" indicates that dystonia is activated by a voluntary task. Activation by voluntary movements facilitates the detection of dystonia that is not observed at rest, or increases the intensity of dystonia when it is too mild to be unequivocally recognized. The activating voluntary movement may vary from non-specific to highly task-specific. Occupational dystonia occurs when a specific occupational task (i.e., a motor task) is performed. Task specificity is a feature of mild forms of dystonia, which may be lost with disease progression. Primary writing tremor was first described in a patient who complained of jerking of the right forearm when writing [17]. Despite its name, this is considered a task-specific dystonia where the movement resembles tremor due to its rhythmicity.

Similarly to movements, dystonic postures may also be activated by specific voluntary motor tasks. Dystonic movements and postures may be alleviated by some specific voluntary movements, also called *gestes antagonistes*, or by "sensory tricks" [18,19]. Their presence strongly supports the diagnosis of dystonia [20] (Figure 2, below). They are thought to inhibit the cortical overflow associated with dystonia at the central level [21]. The two terms hint at different pathophysiological mechanisms: performing a highly specific voluntary movement may interfere with the outflow of motor programs from the basal ganglia, thus inhibiting dystonia (*gestes antagonistes*); on the other hand, sensory afferents may inhibit the clinical emergence of dystonia (sensory tricks) [22]. Thus, *gestes antagonistes* and sensory tricks do not merely oppose a voluntary movement to the involuntary movement.

Patients often automatically select *gestes antagonistes* when dystonic movements are at their peak; this is not an exception to the general rule that voluntary movements, particularly purposeful skilled actions, aggravate dystonia, because *gestes antagonistes* and sensory tricks are very specific motor tasks that must be performed very accurately in order to be efficacious. The amelioration of dystonia with activity has also been termed "paradoxical dystonia" [23]: this is a confounding expression whose usage is discouraged. The *gestes antagonistes* normally involve a body part that is different from (and often contiguous with) the one affected by the dystonia that is alleviated.

3. Differential diagnosis of dystonia

The EFNS MDS-ES task force has provided a number of recommendations on the clinical diagnosis of dystonia [4]. The diagnosis and classification of dystonia are highly relevant for providing appropriate management, prognostic information, genetic counseling and treatment. Given the lack of specific diagnostic tests, expert observation is recommended. Referral to a movement disorders expert increases the diagnostic accuracy [24]. Neurological examination alone allows the clinical identification of primary dystonia and dystonia-plus, but not the distinction between the different etiological forms of heredodegenerative and secondary dystonias.

The primary nature of primary dystonia requires the exclusion of secondary causes. Following the clinical evaluation, there is a long list of potential laboratory investigations to be performed, which should be selected based on probability criteria [25]. When a patient presents with typical features, as a rule, laboratory and neuroimaging examinations are limited to a minimal list. An MRI brain scan is sufficient to exclude secondary causes or heredodegenerative disorders. Cervical MRI may be useful when atlanto-axial subluxation, syringomyelia, Arnold–Chiari malformation, or congenital Klippel–Feil syndrome are suspected. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging have no practical clinical use in primary dystonias, and should be considered for research purposes only. Electromyography (EMG) and electroneurography (ENG) can be used to confirm a diagnosis of dystonia by means of physiological criteria; magnetic resonance spectroscopy is helpful in suspected metabolic disease. The suspicion of a metabolic disease should be limited in most instances to cases with an early onset or

with atypical features (e.g., hepatic disease, anemia, dyslipidemia). Tissue biopsies (e.g., skin, conjunctivae, skeletal muscle, nerve, vascular smooth muscle, neurons obtained from rectal biopsy) are useful in selected cases. Slit-lamp examination of the eye allows finding the Kayser–Fleisher ring; observation of the *fundus oculi* allows the detection of pigmentary retinal degeneration, or optic nerve atrophy.

Several inherited conditions may present with dystonia, such as Huntington's disease, Parkinson's disease, Wilson's disease, and tics. In most cases, the differential diagnosis with primary forms is easy, as accompanying symptoms or history will provide sufficient clues. Still, in a limited number of cases it is useful to perform genetic testing to rule out Huntington's disease, spinocerebellar ataxias (SCAs), dentato-rubro-pallido-luysian atrophy, mitochondrial diseases, neuroacanthocytosis, Wilson's disease, pantothenate kinase-associated neurodegeneration (PKAN), dopa-responsive dystonia (DRD), or early-onset parkinsonisms (PARK2, PARK7). Only three primary dystonias can be diagnosed by direct genetic testing (DYT1, DYT5-GCH1, DYT11-SGCE); however, when patients with primary dystonia belong to a large family pedigree, it is possible to investigate linkage with the DYT6, DYT7 or DYT13 loci. Secondary dystonia provoked by birth injury should be ruled out in all cases with an early onset: a detailed history and – if available – the consultation of clinical charts of pregnancy and birth should exclude all possible causes of secondary dystonia. In infantile cerebral palsy, onset of dystonia is usually earlier than in primary generalized dystonia, and often other neurological abnormalities (such as spasticity, mental retardation, or seizures) are evident on examination. Laboratory tests should exclude metabolic diseases and Wilson's disease.

A number of laboratory tests are available to support the clinical diagnosis, the most important of which is DYT1 testing. According to the EFNS/MDS-ES task force [4], diagnostic DYT1 testing in conjunction with genetic counseling is recommended for patients with primary dystonia with an onset before the age of 30 years [26]. Diagnostic DYT1 testing in patients with onset after age 30 years may also be warranted in those having an affected relative with an early onset [26,27]. Diagnostic DYT1 testing is not recommended in patients with onset of symptoms after the age of 30 who either have focal cranial–cervical dystonia or have no affected relative with early onset dystonia [26,27]. Diagnostic DYT1 testing is not recommended in asymptomatic individuals, including those under the age of 18, who are relatives of familial dystonia patients. Positive genetic testing for dystonia (e.g. DYT1) is not sufficient to make a diagnosis of dystonia unless clinical features show dystonia [26,28].

A diagnostic levodopa trial is warranted in every patient with early-onset dystonia without an alternative diagnosis to rule out levodopa-responsive dystonia [29]. Individuals with myoclonus affecting the arms or neck, particularly in the case of a family history suggesting autosomal dominant inheritance, should be tested for the DYT11 gene [30]. Neurophysiological tests are not routinely recommended for the diagnosis or classification of dystonia; however, the observation of abnormalities typical of dystonia is an additional diagnostic tool in cases where the clinical features are considered insufficient to make a diagnosis [31,32]. Brain imaging is not required routinely when there is a confident diagnosis of primary dystonia in adult patients, because a normal study is expected in primary dystonia [33]. Brain imaging is necessary for the screening of secondary forms of dystonia, particularly in the pediatric population due to the broader spectrum of dystonia at this age [34]. MRI is preferable to CT, except when brain calcifications are suspected. There is no evidence that more sophisticated imaging techniques (e.g., voxel-based morphometry, diffusion-weighted imaging, functional MRI) are currently of any value in either the diagnosis or the classification of dystonia.

3.1. Diagnostic algorithm

Figure 2 provides a flow chart for the clinical recognition of dystonia. This flow chart is particularly applicable to primary and dystonia-plus forms, either focal, segmental or generalized. However, the appropriateness of the diagnosis relies much on the experience of the clinician and on the agreement among different evaluators. This allows ruling out other involuntary movements (such as tics, myoclonus or tremor) or even a psychogenic movement disorder [35]. Once dystonia is recognized, its primary nature must be ascertained.

Electrophysiological testing can support the clinical diagnosis in patients who have clinical features of dystonia, and allow the detection of subclinical abnormalities.

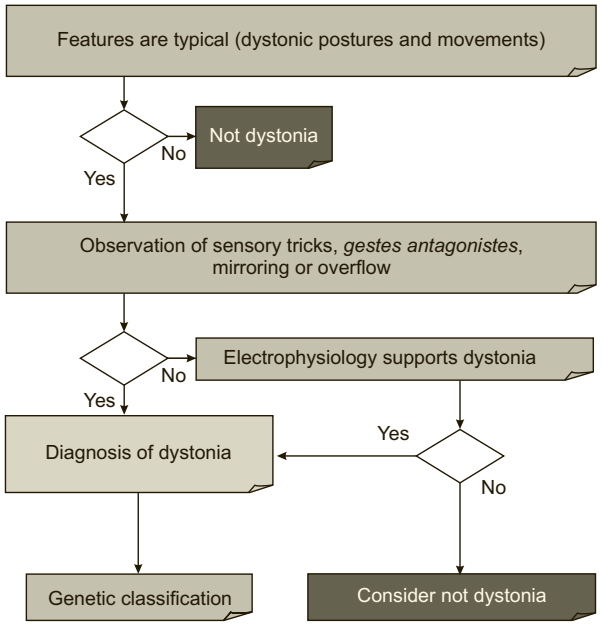

Fig. 2. Flow chart for the clinical diagnosis of dystonia, based on the recognition of its characteristic clinical features.

Excessive co-contraction of antagonistic muscles is one of the physiologic hallmarks of dystonia [36]. In patients who do not have clinically evident overflow, EMG examination may reveal an overflow of contractions to adjacent or remote muscles, which is particularly noticeable during a voluntary movement of the affected limb. The third main physiological characteristic of dystonia is the paradoxical contraction of passively shortened muscles (Westphal phenomenon), which is however not specific for dystonia and is also seen in spasticity and in parkinsonian disorders. In some patients with focal or segmental dystonia there is no EMG-recordable involuntary muscle activity at rest, but in almost all patients with generalized dystonia, involuntary muscle contractions usually persist, even at rest [36]. In addition, some patients have an abnormal reciprocal inhibition, as shown by reflex studies [37].

All the genetic forms of primary dystonia commonly present with a typical combination of dystonic movements and postures, show the activation and deactivation phenomena described above and can be confirmed by electrophysiological testing. The observation of a fixed dystonia, instead, clearly points to a non-primary, likely non-genetic, cause of dystonia [38], although cases of primary fixed dystonia have been reported [39].

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Conflict of Interest statement

None declared.

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