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The clinical expression of primary dystonia

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■ **Abstract** Dystonia (from the Greek, “altered muscle tone”) 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 generalised dystonia. Dystonia arising in childhood tends to progress to a generalised form; adult-onset dystonia, instead, is often focal or segmental. Dystonic

movements have 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 requires the observation of a consistent clinical picture.

■ **Key words** dystonia · diagnosis · clinical features · genetics

Introduction

The term dystonia was introduced in the twentieth century to describe patients with severe generalised dystonia, who were supposed to have an alteration of muscle tone (hence the etymology of this word) [1]. The clinical spectrum of dystonia is broad, yet this is one of the most under-recognised among movement disorders. Historically, the term dystonia has been used extensively by some authors to encompass postural abnormalities observed in spastic paralysis or fixed postural abnormalities [2]. The current definition of dystonia, which is based on the physiological features observed in cases of generalised dystonia [3], depicts “a syndrome of sustained muscle contractions usually producing twisting and repetitive movements or abnormal postures” [4, 5]. The resulting involuntary movement is bizarre and the patients feel pilloried by their weird quaintness; health professionals must not undervalue the resulting stigma. Most patients with dystonia have an associated psycho-

logical disturbance [6], and it is difficult to ascertain to what extent this is a consequence of the movement disorder [7, 8].

Usage of the term dystonia has long remained restricted to severe generalised forms; whereas focal forms have been described as independent movement



Fig. 1 The features of dystonia have struck the imagination of artists more than other motor disturbances. In Dante's *Inferno* (circa 1315) seers are described as having their heads twisted backward (here shown in a miniature from the atelier of Pacino di Bonaguida, National Library, Florence). It is likely that the author was inspired by the observation of patients with cervical dystonia [51]

disorders with specific medical names (Table 1). Until recently, it has been also affirmed that some cases of dystonia, particularly occupational dystonias, are psychogenic [9]. This has delayed the understanding that the clinical spectrum of dystonia is very wide, ranging from task-specific focal forms, to segmental or generalised forms. The common denominator of such remarkably variable clinical range is the occurrence of co-contraction of antagonistic muscles and overflow into extraneous muscles, as a result of basal ganglia dysfunction [10].

To organise the clinical and aetiological heterogeneity of dystonia various classifying schemes have been proposed [5, 11–13]. The clinical features can be summarised by using three descriptors: (a) age at onset of symptoms, (b) distribution or body regions affected, and (c) aetiology (Table 2). The first two categories are independent, yet closely tied to disease severity: the earlier the onset the more likely dystonia is to spread and lead to significant disability [14].

The present review will highlight the clinical features of primary dystonia that are relevant for the purpose of a clinical diagnosis. Although the same features can also

be observed in other forms of dystonia (such as secondary dystonias or dystonia seen in heredo-degenerative diseases), they constitute the clinical hallmark of primary dystonias. The grounds for the observed clinical phenomenology reside mainly in the pathophysiology and the genetic make-up that cause the appearance of dystonia. A complete analysis of these aspects would fall beyond the limited space of the present review.

Basic clinical features

Fahn [12] noted that the abnormal movements occurring in patients with dystonia are diverse, with a wide range in speed, amplitude, rhythmicity, torsion, forcefulness, and distribution in the body and varied relationship depending on whether the patient is at rest or engaged in voluntary motor activity. The involuntary movement associated with dystonia is often variable within months or years and from one subject to the other. However, during a given period of observation, and in each affected individual, dystonia is distinctively consistent and predictable. The occurrence of muscle

Table 1 Terminology used to describe dystonia

Terminology	Dystonia type
Blepharospasm	Focal: involves the upper face and, particularly, the orbicularis oculi muscle.
Spasmodic (or “spastic”) dysphonia	Focal: involves the vocal folds.
Writer’s cramp	Focal: involves the upper limb.
Torticollis	Focal: involves the cervical region.
Camptocormia	Focal: involves the axial musculature causing a forward bending of the trunk.
Scoliosis	Focal: involves the axial musculature causing torsion of the spine.
Meige’s syndrome	Segmental: affects the upper and lower facial muscles.

Table 2 Classifications of dystonia

By age at onset
• Early onset (≤ 21 years): usually starts in a leg or arm and frequently progresses to involve other limbs and the trunk. • Late onset (> 21 years): usually starts in the neck (including the vocal folds), the cranial muscles or one arm. Tends to remain localised with restricted progression to adjacent muscles.
By distribution
• Focal: single body region (e. g., writer’s cramp, blepharospasm) • Segmental: contiguous body regions (e. g., cranial and cervical, cervical and upper limb) • Multifocal: non-contiguous body regions (e. g., upper and lower limb, cranial and upper limb) • Generalised: both legs and at least one other body region (usually one or both arms)
By cause
• Primary (or idiopathic): dystonia is the only clinical sign and there is no identifiable exogenous cause or other inherited or degenerative disease. Example: DYT1 dystonia. • Dystonia plus: dystonia is a prominent sign, but is associated with another movement disorder. There is no evidence of neurodegeneration. Example: myoclonus-dystonia (DYT11). • Heredo-degenerative: dystonia is a prominent sign, among other neurological features, of a heredo-degenerative 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 tumour, off-period dystonia in Parkinson’s disease.

hypertrophy is also an indicator of the prevalent involvement of a specific set of muscles. A distinguishing clinical feature is the occurrence of dystonic movements and postures that are combined to create a sustained postural twisting [4, 15]. 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. For example, patients with cervical dystonia may show isolated neck posturing for years before dystonic neck movements become apparent. By contrast, sustained posturing not evolving toward mobile dystonia often indicates a secondary form.

■ Dystonic postures

Postures flex or twist a body part along the main axis, are associated with a sensation of rigidity and traction and are primarily responsible for pain. Dystonic postures are directional and force the involved body region into an abnormal position that is consistently present. Dystonia may produce quite bizarre posturing of the affected body part. The variety of head postures observed in cervical dystonia has led to the development of a specific terminology (Table 3). As already mentioned, dystonic postures may appear some months or few years before dystonic movements are seen.

In axial dystonia postural abnormalities are often a prominent feature, owing to the rare occurrence of dystonic movements in the trunk. Predominantly postural forms of axial dystonia include scoliosis and camptocormia. Primary scoliosis occurs in adolescence in 80 % of cases and may be hereditary; as a rule, it is not associated with signs of dystonia in other body regions [16], although it may be the presenting sign of primary torsion dystonia [17]. The term camptocormia has been used to indicate a forward-bent trunk [18], which can be due to a variety of causes. Dystonic camptocormia is a sustained postural dystonia that progressively bends the trunk forward and is induced or aggravated by standing and walking [19]. A progressive bending of the trunk laterally, occurring while standing, has been called the Pisa

syndrome, for resemblance with the well known leaning tower of Pisa [20].

Usually, pain is not a prominent feature of dystonia, except for cervical dystonia [21] and some secondary forms. Dystonic postures, rather than movements, cause pain; the higher frequency of pain in cervical dystonia, compared with other primary forms of dystonia, may be due to the bigger size of the involved muscles, to stronger forces, or to a higher number of pain receptors [21]. In addition, pain is particularly common in some secondary forms of dystonia, such as off-period dystonia in Parkinson's disease, where rigidity and dystonia occur in combination [22]. In these cases, pain may also be of central or myofascial origin [23].

■ Dystonic movements

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 posture assuming movements (e.g., ulnar deviation, plantar flexion, vocal fold adduction, eye closure).

Dystonic movements are occasionally rhythmic but most often arrhythmic. When rhythmic, they are difficult to differentiate from non-dystonic essential tremor. For example, the quick, repetitive, jerks observed in cervical dystonia may mimic head tremor. Patients with isolated action tremor of the head or the upper limbs, who do not have a definite family history, may develop unequivocal signs of dystonia only many years after onset [24]. Aside from their directional character, clinical features indicating rhythmic dystonia, rather than essential tremor, include: irregularity, the presence 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" [25–27]; when slow and distal they match the description of athetosis [28].

Table 3 Postural abnormalities observed in cervical dystonia have specific names

Denomination	Head movement
Torticollis	Head rotation to the right or to the left
Antecollis	Forward head flexion
Retrocollis	Backward head extension
Laterocollis	Head tilt to either side
Antepulsion	Shift forward of the head
Retropulsion	Shift backward of the head
Lateropulsion	Lateral shift

Box 1**Essential tremor or primary dystonia?**

Patients with focal or generalised dystonia may present with isolated action tremor, sometimes preceding the development of dystonia by several years or longer [24, 52–54]. In many patients, dystonic movements may bear a resemblance to action tremor [55]. Therefore, tremulous dystonic patients can be misdiagnosed as having essential tremor. This “dystonic tremor” can be difficult to distinguish from essential tremor, particularly in patients with task-specific or focal dystonia, such as in upper limb or cervical dystonia [56]. Dystonic tremor is frequently misdiagnosed as co-existent essential tremor [55, 57], also because both conditions may present a familial transmission. Some retrospective studies have shown dystonia in as many as half of all patients presumed to have essential tremor [58], although a prospective study of relatives of probands with familial tremor revealed no dystonia [59]. Familial essential tremor does not link to the DYT1 [60] or to other dystonia loci.

Unlike tics that 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 that make them assume a “semi-voluntary” or at least intentional nature not usually observed in dystonia. In people with excessive blinking it may be difficult to recognise 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 [29].

Additional clinical features

Dystonia is not a static phenomenon. Changes in the pattern of muscle activation occur during the course of the disease and also following specific manoeuvres that have diagnostic value. For example, in patients with cervical dystonia, the initial schema of botulinum toxin injections needs to be progressively adapted to follow the changing pattern of muscle activity [30]. The ability to aggravate or relieve dystonia by using specific physical signs has diagnostic value in many cases.

■ 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 occurring in dystonic patients, mirroring can be considered as a minimal expression of focal dystonia that is observed in otherwise unaffected body regions. The detection of overflow and mirroring is a relevant clinical exercise, aimed particularly at [1] predicting whether symptoms are expected to progress and involve newer body parts [2], identifying subjects with minimal affections, who are members of families with dystonia.

The severity of dystonia is variable from one case to the other. In some patients, the clinical features are evident and severe enough to allow a diagnosis by simple observation. In others, the clinical features become evident when the patients are requested to perform certain voluntary movements that activate dystonia. The term “action dystonia” indicates that dystonia is activated by a voluntary task. Activation by voluntary movements allows to detect dystonia when it is not observed at rest or to increase its intensity when it is too mild to be unequivocally recognised.

The activating voluntary movement may vary from non-specific to highly task-specific (Fig. 2). Occupational dystonia occurs when a specific occupation (i.e., a motor task) is performed. The most common task-specific dystonias are: musician’s cramp (e.g., upper arm dystonia with bowing, hand dystonia with piano playing or guitar picking, lip and tongue dystonia with playing brass or woodwind), typist’s cramp, golfer’s yip, or card dealer’s hand dystonia. Particularly in the upper limb, dystonia may appear solely when a specific fine motor task is performed. For example, a musician with a task-specific cramp activated by piano playing may have no motor difficulties with handwriting, or vice versa. Task specificity is a feature of mild forms of dystonia, which may be lost with progression. For example, primary dystonia in children may begin as an action dystonia that is evident on walking forward but less apparent walking backwards or running. With progression over time dystonia may become evident whenever the patient walks or even during standing.

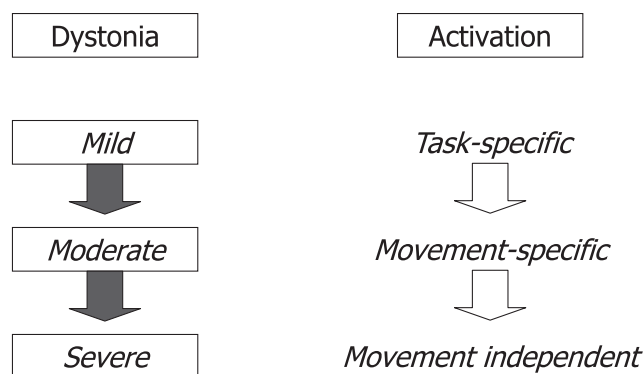


Fig. 2 Task specificity is typically observed in mild focal dystonia and it tends to vanish with progression in severity and with the extension to a generalised form

Primary writing tremor was first described in a patient who complained of jerking of the right forearm on writing [31]. Despite its name, this is considered a task-specific dystonia where the movement resembles tremor due to its rhythmicity. Isolated primary writing tremor has been observed in subjects belonging to dystonia families [32] and has electrophysiological features in common with dystonia [33].

Similarly to dystonic movements, dystonic postures may also be activated by specific voluntary motor tasks.

■ Transiently improving dystonia

Dystonic movements and postures may be alleviated by some specific voluntary movements, also called *gestes antagonistes*, or by sensory tricks [34, 35]. Their observation strongly supports the diagnosis of dystonia [36]. They are thought to inhibit at the central level the cortical overflow associated with dystonia [37] and their finding is a clinical sign for the diagnosis of dystonia. The two terms hint at different pathophysiology: performing a highly specific voluntary movement may interfere with the outflow of motor programmes from the basal ganglia thus inhibiting dystonia (*gestes antagonistes*); on the other hand, sensory afferents may inhibit the clinical emergence of dystonia (sensory tricks) [38]. Thus, *gestes antagonistes* and sensory tricks do not merely counteract the involuntary movement. An example is provided by a patient with axial dystonia (campocormia), whose trunk naturally bent forward as he proceeded (action dystonia). When he kept his dog on the lead, the trunk straightened up swiftly, rather than bending further, as soon as the dog pulled on the leash (sensory trick).

Patients often automatically select *gestes antagonistes* when dystonic movements are at their peak; this can be regarded as an exception to the general rule that voluntary movements, particularly purposeful skilled actions, aggravate dystonia, either mobile or fixed. For that reason, the amelioration of dystonia with activity has also been termed “paradoxical dystonia” [39]. The usage of this confounding expression is, however, to be discouraged. The *gestes antagonistes* normally involve a body part different from (and often contiguous with) the one affected by dystonia that is alleviated. Examples of task-specific alleviation of dystonia are movements of the upper limb (such as stretching the arm in a particular way or holding a newspaper with the arms outstretched) that relieve cervical dystonia or the observation that speaking or chewing alleviates blepharospasm or other forms of cranial dystonia. By contrast, sensory tricks are usually tactile or sensory manoeuvres (such as touching the side of the cheek or occiput to relieve torticollis), but may include other sensory modulators such as ambient sound [40]. Also, some patients can obtain benefit simi-

lar to that obtained from performing their trick by just imagining it [34]. Other factors or states that improve or relieve dystonic movements include relaxation, hypnosis, and sleep [41].

Supportive laboratory examinations

Electrophysiological testing supports the clinical diagnosis by revealing specific features in patients with clinical features of dystonia. In addition, physiology allows detecting sub-clinical abnormalities. Inappropriate co-contraction of antagonistic muscles is one of the physiological hallmarks [42]. In patients who do not have clinically manifest overflow, EMG examination may allow one to detect an overflow of contractions to adjacent or remote muscles, which is particularly noticeable during a volitional movement of the affected limb. The third main physiological characteristic of dystonia is the paradoxical contraction of passively shortened muscles (Westphal phenomenon); that 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 generalised dystonia, involuntary muscle contractions usually persist, even at rest [42]. In general, patients have abnormality of inhibitory reflexes, but the relationship between this abnormality and the appreciable clinical signs of dystonia is not clear [43].

Brain morphology (e.g., CT or MRI) is normal in primary dystonia; however brain-imaging abnormalities are useful findings for the diagnosis of secondary dystonias. For example, MRI can allow the recognition of focal brain lesions, Wilson’s disease or pantothenate kinase associated neurodegeneration by detecting specific signal abnormalities in the brain. PET imaging has shown that primary and secondary dystonias are associated with an increase in activation of the rostral premotor areas and prefrontal cortex and with metabolic changes in the basal ganglia [44–47]. These features, however, are not used for diagnostic purposes.

■ Genetic testing

The clinical diagnosis of dystonia can be confirmed by genetic testing. Direct testing of genes causing dystonia is available for a number of forms. So far, only one primary dystonia gene, the DYT1 gene, has been identified and can be tested directly for mutations. The other known genes are responsible for: (1) dystonia-plus syndromes, where dystonia is associated with other neurological features (e.g., dopa-responsive dystonia), or (2) heredo-degenerative diseases causing dystonia (e.g., pantothenate kinase associated neurodegeneration or

Hallervorden-Spatz disease). Direct analysis of known dystonia genes may require a significant amount of laboratory work and has variable costs, depending on the number of known mutations and the size of the gene tested. For example, testing of the DYT1 mutations is simple and inexpensive; by contrast, analysis of the DYT5 gene is time consuming and expensive. A common feature of all primary dystonia genes so far identified is the reduced penetrance, that never exceeds 40 % [48, 49]. This means that the status of asymptomatic dystonia

gene carrier is more likely than that of affected carrier. Thus, the detection of a mutation for a dystonia gene is not sufficient to label a patient as affected by dystonia [50]; a consistent clinical picture, encompassing the clinical features highlighted above, must also be observed.

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