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Dystonia: phenomenology

Mark S. LeDoux*

Departments of Neurology, and Anatomy and Neurobiology, University of Tennessee Health Science Center, Memphis, TN, USA

SUMMARY

In 1984, dystonia was defined by an ad hoc committee of the Dystonia Medical Research Foundation as a syndrome of involuntary, sustained muscle contractions affecting one or more sites of the body, frequently causing twisting and repetitive movements, or abnormal postures. In 2011, dystonia remains a purely clinical diagnosis. Primary dystonia includes syndromes in which dystonia is the sole phenotypic manifestation with the exception that tremor can be present as well. Primary dystonias are typically mobile and may show task specificity. Fixed dystonias are often psychogenic or associated with complex regional pain syndrome. Fixed dystonia may also be the terminal consequence of long-standing, inadequately-treated, severe appendicular or cervical dystonia. The vast majority of primary dystonias have their onset in adults. Late-onset, primary, focal dystonia, particularly blepharospasm, may spread to affect other anatomical segments. Patients with focal dystonia may also exhibit spontaneous remissions that last for years. Although sensory tricks are commonly reported by patients with primary dystonia, they have also been described in subjects with secondary dystonia. Another important sensory aspect of dystonia is pain which is relatively common in cervical dystonia but also reported by many patients with masticatory dystonia, hand–forearm dystonia and blepharospasm. In conclusion, “dystonia” can be used to delimit a clinical sign or loosely define a neuropsychiatric sensorimotor syndrome.

Keywords

Dystonia; Geste Antagoniste; Anxiety; Pain; Tremor

1. Introduction

Dystonia, including primary dystonia, affects virtually all racial and ethnic groups [1]. However, certain genetic forms of dystonia may be more common in certain ethnic groups. Examples include the DYT1 *TOR1A* ΔGAG mutation in individuals of Ashkenazi Jewish ancestry and DYT6 dystonia in Amish-Mennonites. Adult-onset focal dystonias such as cervical dystonia may be more common in Caucasians of European descent [2]. Late-onset primary dystonia affects from 600 to 3000 per million in Europe [3]. Prevalence estimates for early-onset primary dystonia range from 2 to 50 cases per million. In comparison,

*Correspondence: Dr. Mark S. LeDoux, University of Tennessee Health Science Center, Department of Neurology, 855 Monroe Avenue, Link Building-Suite 415, Memphis, Tennessee 38163, USA. Tel.: +1 901 448 1662; fax: +1 901 448 7440. mledoux@uthsc.edu (M.S. LeDoux).

secondary dystonia and dystonia occurring in association with heredodegenerative diseases is probably much more common than primary dystonia in most populations.

Dystonia is characterized by (1) abnormal co-contraction of agonist and antagonist muscle groups, (2) abnormal prolongation of EMG bursts in muscles normally required for a specific motor act, (3) impaired volitional control of a group of somatotopically contiguous muscles, and (4) impaired inhibition of spinal and brainstem reflexes beyond the somatotopic extent of clinical involvement. Most commonly, however, dystonia is an observational diagnosis made without physiological or genetic testing. Tremor is included in this definition since rhythmic activation of contiguous muscle groups can be seen in a significant fraction of patients with focal, segmental and generalized dystonia. Spontaneous remissions in patients with focal dystonia, particularly those with cervical dystonia and blepharospasm, may last years and suggest that dystonia is the consequence of aberrant neural networks becoming trapped in local minima rather than irreversible cellular pathology.

Most forms of late-onset focal dystonia are more common in women [4,5]. The male:female ratio is approximately 1:1.5–2 for most forms of craniocervical dystonia. This male:female ratio was reversed in some, but not all series of hand–forearm dystonia. Similarly, the penetrance of DYT5 due to *GCH1* mutations is higher in females. Gender may exert effects on age of onset in myoclonusdystonia due to SGCE mutations [6].

2. Classification

Dystonia can be classified by age of onset, distribution and etiology [3,7]. Age of onset can be divided into early (<20 years) and late (>20 years) [3] and guides the clinician to underlying etiologies. For example, DYT1 dystonia typically presents around 10 years of age with distal lower extremity dystonia. In contrast, the mean age of onset for primary focal dystonias of the head and neck is approximately 50 years [5,8]. Focal and segmental distributions are most common in adults and include cervical dystonia, blepharospasm, masticatory dystonia, laryngeal dystonia and segmental craniocervical dystonia. Generalized dystonia is defined by involvement of a leg, the trunk and at least one other body part. Hemidystonia is usually secondary to structural lesions of the CNS. Etiological categories include primary dystonia, secondary dystonia, dystonia-plus, heredodegenerative diseases with dystonia, psychogenic dystonia and pseudodystonia. Pseudodystonia includes dystonia mimics associated with abnormal postures such as atlantoaxial dislocation. The dystonia-plus category is distinct from both the primary dystonias and heredodegenerative diseases with dystonia. Dopa-responsive dystonia (DRD: DYT5) falls within the dystonia-plus category. Characteristically, patients with DRD respond dramatically to very small doses of levodopa, a clinical finding which distinguishes DYT5 from the other hereditary dystonias.

In many neurodegenerative diseases, dystonia may be either a prominent or presenting feature. In these patients, characteristic neurological and neuroimaging findings usually permit an accurate diagnosis. In particular, the presence of parkinsonism, dementia, autonomic dysfunction, and/or oculomotor abnormalities in the hereditary and neurodegenerative diseases with dystonia set these disorders apart from the primary

dystonias. Occasionally, however, dystonia can be an isolated, prominent or presenting feature of numerous neurogenetic disorders ranging from spinocerebellar ataxia type 2 [9] to mutations in PINK1 [10].

3. Mobile versus fixed dystonia

The concept of fixed dystonia and its possible association with peripheral trauma has been a controversial topic for many years. The mobile and fixed dystonias may be driven by largely distinct pathophysiological processes [11,12]. Fixed dystonia is more common in females and usually affects the limbs with occasional involvement of the neck or jaw [13]. A significant percentage of patients with fixed dystonia meet criteria for complex regional pain syndrome and/or have one or more manifest psychiatric disorders. In general, fixed dystonia responds poorly to oral pharmacotherapy and injections of botulinum toxin but may improve with physiotherapy and psychotherapy.

4. Dystonia and tremor

Appendicular tremors may be seen in early-onset DYT1 (*TOR1A*) or DYT6 (*THAP1*) dystonia. Rhythmic movements and rhythmic EMG bursts are particularly common in those body parts affected in late-onset cervical and hand–forearm dystonia [14]. Appendicular tremors, largely non-dystonic, are also common in patients with isolated cervical and laryngeal dystonia [15,16].

Dystonic tremor remains poorly defined and can be difficult to distinguish from essential tremor and other action tremors. Certain clinical clues are helpful, however. Dystonic tremors usually increase in amplitude with attempts to move in opposition to the direction of dystonic contractions. Dystonic tremors also tend to show greater variability in burst duration and amplitude than essential tremor and most other action tremors. Dystonic tremors are rarely seen during complete rest. Finally, appendicular dystonic tremor tends to show much greater right–left asymmetry than essential tremor.

Probands with dystonia appear to have an increased family history of tremor [17]. Clustering of dystonia with essential tremor in some pedigrees suggests the strong possibility that different biological subtypes of essential tremor exist in the population and share common genetic etiologies with a subset of primary dystonia cases [18]. In one study, focal or segmental dystonia was present in 98 out of 463 patients with essential tremor [18].

5. Patterns of anatomical involvement and spread

In general, the relationship between anatomical site of onset and age of onset obeys a caudal-to-rostral gradient. Distal leg dystonia typically begins in childhood with inversion and plantar flexion at the ankle and progresses rostrally whereas blepharospasm usually appears during the 5^{th} or 6^{th} decade of life. Exceptions exist, however, and leg dystonia may appear in adults without foot inversion [19]. In one large clinical cohort of 1446 subjects with primary non-DYT1 dystonia, mean ages of onset for blepharospasm (58 years), oromandibular dystonia (53 years), spasmodic dysphonia (46 years), cervical dystonia (45 years) and hand–forearm dystonia (35 years) were consistent with a caudal-to-rostral

gradient [20]. The caudal-to-rostral gradient also applies to DYT1 (*TOR1A* ΔGAG) dystonia [21,22].

The anatomical distribution of dystonia can range from severe involvement of all limbs, trunk, and most craniocervical regions, to discrete involvement of single muscles during specific motor acts. For instance, inspiratory laryngeal dystonia is typically due to isolated involvement of the thyroarytenoid muscles during inspiration. Many dystonias show task specificity. Classic examples of task-specific dystonias include writer's cramp and embouchure dystonia. Task-specific dystonias have also been described in professional card dealers, pianists, violinists, typists and golfers.

Focal dystonias may spread from their initial site of onset. Risk for rostral spread is high in early-onset DYT1 dystonia that begins in a leg. Among the late-onset dystonias, risk of spread is highest for blepharospasm. Blepharospasm often spreads to the lower face and masticatory muscles, and, in a smaller subset of patients, to the cervical musculature. The term "segmental craniocervical dystonia" is used to describe the combination of blepharospasm and dystonia of other head and neck muscles [23]. Particular subphenotypes of segmental craniocervical dystonia, such as blepharospasm with apraxia of eyelid opening and anterocollis, may be clinically unique [24].

6. Sensory tricks

Sensory tricks (gestes antagonistes) are a well-known feature of primary dystonia and can also be seen in some patients with secondary dystonias. In one series, sensory tricks were reported in 71% of subjects with blepharospasm and 84% of subjects with cervical dystonia [25]. Sensory tricks provide useful ancillary information for the purpose of establishing a clinical diagnosis and direct the physician towards supplementary treatment options. For example, oral appliances can be particularly effective for subjects with masticatory dystonia [26]. In some patients, simply thinking about the trick (interoceptive stimulus) helps to alleviate dystonia [27]. "Reverse" sensory gestes have also been reported. In one patient, for instance, craniocervical dystonia was precipitated by putting on glasses with a ribbon [28].

7. Pain and psychiatric co-morbidities

Although commonly associated with cervical dystonia, significant pain may be reported by patients with blepharospasm, masticatory dystonia, and limb dystonia. In some patients with cervical dystonia, pain is much more debilitating than abnormal head postures [29]. Pain intensity often correlates poorly with the severity of dystonic contractions or amplitude of involuntary movements. Painful photophobia in blepharospasm is relatively common and may be sympathetically maintained [30].

Subjects with primary focal dystonia may have more obsessive-compulsive tendencies and a higher frequency of depressive disorders than matched control groups [31,32]. In a significant percentage of subjects, depression may pre-date the onset of dystonia. Premorbid psychiatric disorders are not common in subjects with early-or adult-onset limb dystonia.

8. Family history of dystonia

A positive family history with either phenotypic concordance or discordance is an important aspect of the phenomenology surrounding the primary dystonias. In most movement disorders clinics, the majority of subjects with dystonia are adults with primary focal or segmental involvement, and 8–27% of these late-onset probands have at least one first-degree relative with dystonia [5,33–36]. These percentages are consistent with autosomal dominant inheritance of rare sequence variants of low to moderate penetrance [5].

In several clinical series, first-degree relatives were subjected to examination [37–39]. Within these reported families, phenotypic concordance/discordance was approximately 50%/50%. An example of phenotypic discordance would be the presence of blepharospasm in a proband and cervical dystonia in one of the proband's siblings. Although late-onset primary dystonia has a considerable "heritable" component, large pedigrees adequately powered for linkage analysis are uncommon and only a few have been described in the literature [1,40].

9. Conclusions

Dystonia is a poorly-defined multifarious neuropsychiatric sensorimotor disorder. The non-motor sensory and psychiatric aspects of dystonia may demand considerable attention in a subset of patients. Dystonia is not a static process and may resolve spontaneous or spread to involve additional body parts. Focal dystonias may be localized manifestations of more generalized CNS dysfunction.

Acknowledgments

Acknowledgements/Conflict of interests

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