Dystonia

Five new things

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Summary

There has been considerable progress in our understanding of dystonia over the last century. Growing recognition of dystonia has enhanced awareness of its diverse motor phenomenology and brought attention to the importance that nonmotor features may play in this disorder, once considered to be purely motor. Using the latest technologies in human genetics, new genetic links are being discovered at an ever-quicken pace and expanding our knowledge of the disorder's complex pathogenesis. Furthermore, as we gain clearer insight into the pathophysiology of dystonia and an appreciation of the involvement of dysfunction outside the basal ganglia, dystonia has been increasingly viewed as a network disorder. Here we briefly discuss some of the recent noteworthy advances.

The term “dystonia” was first coined in 1911 by the German neurologist Hermann Oppenheim, who surmised that the core defect in a group of individuals with an unusual motor disorder was abnormal muscle tone. While dystonia is no longer thought to stem from a disturbance in muscle tone, how to properly define and characterize the disorder has been debated repeatedly.

A new classification system

An international consensus committee recently sought to revise the definition of dystonia in order to address the limitations of previously proposed definitions. Dystonia was defined as “a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous.”¹ Unique motor phenomenology aspects of dystonia that help distinguish it from other movement disorders were also added to the definition: “Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.”¹ While this revised definition addressed some prior shortcomings, it also sparked some debate. For example, the definition now recognizes that dystonia can manifest as discontinuous and irregular muscle contractions and that abnormal postures in dystonia may be tonic or spasmodic, dynamic or fixed, or any combination of these.

In addition to proposing a revised definition for dystonia, the international consensus committee set out to improve the classification of dystonia. In 1976, Fahn and Eldridge

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first proposed distinguishing primary dystonia with or without a hereditary pattern from secondary dystonia in which there was a known environmental cause or other hereditary neurologic disorder. This classification scheme is still useful today, but an increasing understanding of the various etiologies of dystonia has led to a need for a more detailed system.

The varied manifestations of dystonia have also led to classification schemes based on clinical features. The most popular of these have been classifications by age at onset and body distribution. The frequently used age cutoff of 26 years for early- and late-onset forms of dystonia, however, focused on only DYT1 dystonia. As more genetic forms of dystonia were identified and our knowledge of the relevance of age to the specific causes increased, it became clear that a more refined age categorization was needed. Furthermore, we have a greater appreciation of the varied temporal patterns seen in dystonia and the relevance of this clinical feature to identifying an underlying diagnosis, underscoring the need for an updated classification scheme.

The international consensus committee proposed a restructured classification system for dystonia based on 2 main axes: clinical characteristics and etiology (table 1).¹ The clinical characteristics axis includes the long-standing classification by age at onset and body distribution, but the age at onset is now divided across 5 age groups in order to better distinguish among the varying etiologies that tend to afflict individuals at different ages. The revised classification system also includes a new categorization addressing temporal patterns, which can aid the diagnosis of specific forms of dystonia and point toward an appropriate treatment. The temporal features of dystonia are divided into 2 categories, one that specifies the overall disease course and one for shorter-term variability.

A controversial aspect of the newly proposed dystonia classification system is the elimination of the widely used terms “primary” and “secondary” for describing etiology. While these terms have been useful in the past to distinguish between 2 main etiologic classifications, they lack clarity and have had diminishing utility, in part due to a greater understanding of the diverse dystonia etiologies and increasing recognition of associated neurologic and psychiatric features. The currently proposed approach is therefore to classify dystonia in terms of its associated features. That is, as either *isolated* (the only motor feature except for tremor) or *combined* with other neurologic or systemic manifestations.

The second axis aims to classify the diverse forms of dystonia by etiology. The numerous etiologies of dystonia are grouped based on shared biological mechanisms. This includes grouping dystonia by whether identifiable anatomical changes are present or not and by whether it is inherited, acquired, or idiopathic. Subgrouping delineates the dystonia by inheritance pattern as well as the specific environmental cause when it is acquired. As our understanding of the genetic and environmental contributions advances, reclassification of some dystonias and revision of this classification scheme are likely.

Importance of nonmotor features

Dystonia is defined in terms of its motor manifestations, and isolated (previously *primary*) dystonia has long been considered a purely motor disorder. However, there is an increasing awareness of nonmotor features.^{2,3} As in Parkinson disease, nonmotor symptoms in dystonia such as pain, sleep disturbances, psychiatric symptoms, fatigue, and cognitive impairment can

Table 1 2013 classification of dystonia¹

Axis I: clinical characteristics	Axis II: etiology
Age at onset	Neuropathology
Infancy (0–2 years)	Degenerative
Childhood (3–12 years)	Structural lesion
Adolescence (13–20 years)	No degeneration/structural lesion
Early adulthood (21–40 years)	Etiology
Late adulthood (>40 years)	Inheritance pattern
Body distribution	Autosomal dominant
Focal	Autosomal recessive
Segmental	X-linked recessive
Multifocal	Mitochondrial
Generalized	Acquired cause
Hemidystonia	Perinatal brain injury
Temporal pattern	Infection
Disease course	Drug
Static	Toxic
Progressive	Vascular
Variability	Neoplastic
Persistent	Brain injury
Action-specific	Psychogenic
Diurnal	Idiopathic
Paroxysmal	Sporadic
Associated features	Familial
Isolated	
Combined	
Co-occurring manifestations	

affect quality of life and considerably contribute to disability. As such, neurologists will increasingly need to recognize and address nonmotor features when caring for patients with dystonia, as they can have a big effect on satisfaction with treatments.

In patients with blepharospasm, laryngeal dystonia, and cervical dystonia, eye dryness, throat irritation, and neck discomfort often precede the development of dystonia.³ Pain can affect up to 75% of patients with cervical dystonia and 30% of patients with writer's cramp.^{2,3} Sleep disturbances have also been reported in patients with various focal dystonias, including impaired sleep efficiency and quality, reduced REM sleep, increased awakenings, and an increase in abnormal movements prior to awakening. One recent study of 221 patients with focal dystonia reported impaired sleep quality in 46% of those with blepharospasm and 44% of those with cervical dystonia compared with 20% of healthy controls.⁴ In this study, no correlation was found between sleep impairment and dystonia severity, raising the possibility that sleep abnormalities may be an intrinsic feature of isolated dystonia. Sleep impairment was correlated with depressive symptoms, however, suggesting that depression or the use of antidepressants could be contributing to these results.

The most common psychiatric manifestations associated with dystonia and predictors of a patient's quality of life are disorders of mood. A recent review of larger studies in which a

A mutation in the Cip1-interacting zinc finger protein 1 gene (*CIZ1*) (*DYT23*) was recently identified as causing adult-onset cervical dystonia.

diagnosis was based on a structured clinical interview and standardized criteria found that of 89 patients with focal dystonia, 57.3% had psychiatric disorders, compared to 24.1% of healthy participants and 34.6% of patients with hemifacial spasm.⁵ Arguing against the idea that these psychiatric symptoms are secondary to the motor disorder, the psychiatric disorders started on average 18.4 ± 13.9 years before the onset of dystonia. A number of studies have also reported that depression is more frequent in nonmanifesting carriers of *DYT1* dystonia and that in other forms of dystonia depressive symptoms are not correlated with dystonia severity, further supporting the idea that depression may be an intrinsic feature of dystonia and not simply a reaction to the motor disorder.^{2,3} However, other studies have reported a correlation between treatment-related changes in motor severity and improvement in mood, complicating our understanding of the cause of depression in dystonia.

Although anxiety frequently accompanies depression in dystonia, the relationship of anxiety disorders such as social phobia and obsessive-compulsive disorder to dystonia is less clear. One study reported a 71% lifetime prevalence of social phobia in a cohort of 116 patients with cervical dystonia.⁶ An increased frequency of obsessive-compulsive disorder has similarly been reported for the myoclonus-dystonia syndrome (*DYT11*).⁷ However, an increase in anxiety disorders has not been found more generally in other types of dystonia.

In addition to psychiatric symptoms, a number of studies have investigated cognitive deficits in idiopathic and genetic forms of dystonia. While some important differences in attentional, executive, and visuospatial functions between dystonia patients and controls have been reported, these findings have generally been mild and are potentially confounded by exposure to dopaminergic or anticholinergic therapy or the presence of pain, sleep impairment, or depression.^{2,3} Overall, there is insufficient evidence for clinically relevant cognitive dysfunction in isolated dystonia.

New isolated dystonia genes

Advances in genetics have led to the identification of a rapidly growing number of monogenic causes of isolated dystonia (table 2), and with them an increasing understanding of the pathogenesis of dystonia. First described in 1997, *DYT1* dystonia is a dominantly inherited, early-onset, generalized isolated dystonia caused by mutations affecting TorsinA (*TOR1A*).⁸ *TOR1A* is a member of the AAA+ protein family—ATPases associated with an array of cellular activities—of chaperones and is linked to a variety of cellular structures, including the nuclear envelope, the endoplasmic reticulum, and the cytoskeleton. Despite almost 2 decades of research into the function of *TOR1A*, how mutations in the gene lead to dystonia remains unknown.

A second isolated dystonia, *DYT6*, was identified in 2009. *DYT6* dystonia is an adolescent-onset mixed dystonia caused by a primarily dominantly inherited mutation in the Thanatos-associated protein domain containing apoptosis associated protein 1 gene (*THAP1*).⁹ *THAP1* is a zinc-finger protein involved in regulating gene transcription for a number of target genes.

By combining next-generation sequencing with genome-wide linkage analysis, the number of identified gene mutations that cause isolated dystonia has more than doubled in just the last 2 years. A mutation in the Cip1-interacting zinc finger protein 1 gene (*CIZ1*) (*DYT23*) was

Table 2 Isolated dystonia genes

Inheritance pattern	Disease	Gene	Protein	Putative function
Autosomal dominant	Early-onset generalized dystonia (DYT1)	<i>TOR1A</i>	TorsinA	AAA1 protein, nuclear envelope, endoplasmic reticulum secretory and stress response, regulation of synaptic function
	Adolescent-onset mixed dystonia (DYT6)	<i>THAP1</i>	Thanatos-associated domain-containing apoptosis associated protein 1	Atypical zinc-finger protein (THAP domain is chromatin-binding factor and regulates transcription)
	Adult-onset focal dystonia (DYT7)	Unknown		
	Adolescent-onset multifocal/segmental dystonia (DYT13)	Unknown		
	Adult-onset generalized/multifocal dystonia (DYT21)	Unknown		
	Adult-onset cervical dystonia (DYT23)	<i>CIZ1</i>	Cip1-interacting zinc finger protein 1	Regulation of G1-S cell cycle and DNA replication
	Adult-onset cervical and craniocervical dystonia (DYT24)	<i>ANO3</i>	Anoctamin 3	Calcium-gated chloride channel
	Adult-onset cervical and craniocervical dystonia (DYT25)	<i>GNAL</i>	Alpha subunit of G protein	Interaction with D1 and adenosine 2A receptors
Autosomal recessive	Early-onset generalized dystonia (DYT2)	Unknown		
	Adolescent-onset (DYT17)	Unknown		

recently identified as causing adult-onset cervical dystonia.¹⁰ In addition, mutations in the anoctamin 3 gene (*ANO3*) (DYT24) and the guanine nucleotide-binding protein (G protein), alpha activating activity polypeptide, olfactory type gene (*GNAL*) (DYT25) were identified as causing adult-onset craniocervical dystonia.^{11,12} Despite similar clinical phenotypes, these 3 recently identified genes have distinct functions, including cell cycle regulation (*CIZ1*), a calcium-gated chloride channel (*ANO3*), and dopamine D1 and adenosine A2a receptor signaling (*GNAL*).

The gene mutations causing isolated dystonia reported to date have given us some insight into the molecular mechanisms involved in dystonia, and themes in the molecular pathways that lead to isolated dystonia are beginning to emerge.¹³ For example, mutations in *TOR1A* and *GNAL* both disturb dopamine signaling, which is consistent with other lines of evidence suggesting a role for abnormal dopamine function in dystonia. *TOR1A*, *THAP1*, and *CIZ1* have been shown to be involved in cell cycle control and transcriptional regulation, highlighting that defects in these critical cellular functions could play a key role. Furthermore, *TOR1A* and *THAP1* encode proteins important for nuclear envelope and endoplasmic reticulum function, suggesting that disturbances in their vital cellular roles could be key to understanding the pathogenesis of dystonia.

Figure Representation of the basal ganglia (red) and cerebellar (blue) networks with potential interaction regions in dystonia, including the thalamus and pontine nuclei

Dystonia as a network disorder

Although there is no evidence of neurodegeneration in isolated dystonia, a variety of subtle microstructural changes have been reported. Furthermore, using structural and functional imaging along with other physiologic investigative tools, abnormalities affecting several brain regions have been detected. To account for this diverse set of experimental findings and the growing recognition that brain structures outside the basal ganglia are involved in dystonia, many investigators have proposed that dystonia may be best understood as a network disorder.^{14,15}

That the sensorimotor basal ganglia and associated thalamocortical circuits may play a key role in the pathophysiology of dystonia is supported by a considerable body of evidence. However, a wide array of imaging studies have detected abnormalities beyond these circuits, including a various cortical regions such as the parietal and cingulate cortices, the brainstem, and the cerebellum.^{16,17} Lesion studies also suggest that dystonia can be caused by lesions of the basal ganglia, thalamus, and cortex, as well as of the brainstem, cerebellum, and spinal cord.¹⁶ While studies with animal models clearly provide additional evidence that disturbances to the basal ganglia can induce dystonia,¹⁵ they also provide evidence that disturbances to the cerebellum can cause dystonia.^{15,18}

In a network model, dystonia could result from dysfunction affecting one or more of the brain regions within the network or from abnormal communication between brain regions within the network. As a role for the cerebellum and associated thalamocortical circuits is increasingly recognized, one possibility is that a dysfunctional interaction between basal ganglia and cerebellar networks causes dystonia (figure).¹⁴ The network disorder framework could help explain why a diverse set of cellular pathways implicated by the

Table 3 Currently available botulinum toxin formulations

Generic name	Trade name	Manufacturer	Serotype	Preparation/storage	FDA indications (year approved)
AbobotulinumtoxinA	Dysport	Ipsen, Ltd.	A	Reconstitution of freeze-dried powder/ refrigerated	Cervical dystonia (2009)
IncobotulinumtoxinA	Xeomin	Merz Pharmaceuticals	A	Reconstitution of freeze-dried powder/ room temperature storage	Cervical dystonia (2010), blepharospasm (2010)
OnabotulinumtoxinA	Botox	Allergan, Inc.	A	Reconstitution of vacuum-dried powder/ refrigerated	Cervical dystonia (2000), blepharospasm (1989)
RimabotulinumtoxinB	Myobloc	US WorldMeds	B	Prediluted liquid/ refrigerated	Cervical dystonia (2000)

Abbreviation: FDA = US Food and Drug Administration.

known isolated dystonia genes all lead to dystonic movements. It also helps interpret the myriad of prior imaging findings and findings from animal and lesion studies in dystonia.

The network disorder model for dystonia is a relatively new and broad conceptual paradigm that attempts to accommodate existing evidence regarding the pathogenesis of dystonia. It has added to our evolving understanding of dystonia and helped stimulate the generation of novel testable hypotheses. It remains to be seen whether the network model will inform the development of new treatments for dystonia and remain compatible with future genetic, neuropathologic, animal model, and imaging findings.

New botulinum toxins

Current oral treatment options frequently used to treat dystonia include anticholinergics, baclofen, benzodiazepines, dopamine modulators, and other muscle relaxants.¹⁹ These treatments are largely symptomatic, frequently provide only limited benefit, and can be associated with intolerable adverse effects. Botulinum toxin (BoNT), however, has proven to be an efficacious symptomatic treatment option for many patients (table 3).

BoNT works in dystonia by chemodenervating the injected muscle and producing local, temporary weakness. A total of 7 immunologically distinct toxins have been discovered that all work by interfering with the release of acetylcholine at the presynaptic terminal. BoNT serotype A does this by proteolytically cleaving synaptosomal-associated protein 25 (SNAP-25), while serotype B works by cleaving vesicle-associated membrane protein (VAMP). OnabotulinumtoxinA (Botox) and rimabotulinumtoxinB (Myobloc) both received US Food and Drug Administration (FDA) approval in the United States for cervical dystonia in 2000 (for readers outside the United States, check with local regulatory agencies for approved diagnoses for BoNT products). Two newer brands of serotype A became available in the last few years: abobotulinumtoxinA (Dysport) and incobotulinumtoxinA (Xeomin). AbobotulinumtoxinA has FDA approval for cervical dystonia and incobotulinumtoxinA has approval for cervical dystonia and blepharospasm. While not specifically FDA-approved for other forms of dystonia, BoNT has proven to be safe and efficacious in oromandibular, laryngeal, limb, and truncal dystonia as well.^{19–21}

Poor responses to BoNT in dystonia may occur for a number of reasons, including insufficient dose, inappropriate muscle selection, disease-related changes, and in some cases the development of immunoresistance to the BoNT. The development of actual neutralizing antibodies to BoNT with any of the modern formulations of BoNT and current treatment guidelines,

however, is thought to be rare. Patients who develop resistance to one brand of toxin may regain benefit by switching to a new brand, though the response to the new formulation may also diminish over time. Studies investigating this course of action are largely limited to the use of rimabotulinumtoxinB in dystonia patients with resistance to onabotulinumtoxinA.^{20,21}

Although their structures and mechanism of action vary, it appears that long-term efficacy and side effects are not dramatically different between different toxin formulations.^{20,21} Formal comparisons between them, however, are lacking. Therefore, the decision to choose one brand over another may depend on factors other than safety and efficacy. Preparation and storage requirements vary across different BoNT formulations, which may result in advantages of one product over another depending on a particular practice setting. Prices may also vary across products and geographic regions, so the cost of a particular toxin could be an important consideration. Most manufacturers of BoNT offer copay assistance programs, but program specifics or insurer and regional variations may make one brand more favorable to some patients than others.

One important clinical consideration when switching or using different BoNT formulations is that each possesses its own potency. Great care is required to ensure the proper dosing is used with each individual brand of toxin to avoid medication errors and adverse events. Familiarity with all the BoNT formulations is also useful when facing questions from an increasingly educated patient population.

Dystonia: Five new things

- A revised definition and new classification system has been proposed for dystonia that categorizes knowledge of clinical features to aid in diagnosis and organizes the rapidly increasing knowledge of biological mechanisms to help inform treatment development.
- The ability of nonmotor features in dystonia to affect quality of life is increasingly being recognized and their pathophysiologic implications are starting to be explored.
- Using modern genome sequencing methods, novel isolated dystonia genes are being identified at a swift pace and common molecular pathways are beginning to surface.
- Growing evidence has led to an emerging view of dystonia as a network disorder that arises from dysfunction affecting one or more regions within an interconnected system of brain regions.
- New botulinum toxin formulations have increased the number of choices available for this safe and efficacious therapeutic option for the treatment of dystonia.

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