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Recent Developments in Dystonia

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Abstract

Purpose of review—The dystonias are a family of related disorders with many different clinical manifestations and causes. This review summarizes recent developments regarding these disorders, focusing mainly on advances with direct clinical relevance from the past two years.

Recent findings—The dystonias are generally defined by their clinical characteristics, rather than by their underlying genetic or neuropathological defects. The many varied clinical manifestations and causes contribute to the fact that they are one of the most poorly recognized of all movement disorders. A series of recent publications has addressed these issues offering a revised definition and more logical means for classifying the many subtypes. Our understanding of the genetic and neurobiological mechanisms responsible for different types of dystonias also has grown rapidly, creating new opportunities and challenges for diagnosis and identifying increasing numbers of rare subtypes for which specific treatments are available.

Summary—Recent advances in describing the clinical phenotypes and determining associated genotypes have pointed to the need for new strategies for diagnosis, classification and treatment of the dystonias.

Keywords

Torticollis; blepharospasm; spasmodic dysphonia; writer’s cramp

Introduction

The dystonias are a heterogeneous group of disorders that are defined by the nature of their abnormal movements. They may involve nearly any region of the body, emerge at any age, appear static or progressive, and occasionally co-occur with other neurological or medical problems. Due to their varied clinical manifestations, they can be difficult to recognize and diagnose, particularly the less common or unusual forms.

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Conflicts of interest

The authors report no conflicts of interest.

The underlying causes for the dystonias are equally varied. While some are acquired and others inherited, many are idiopathic. Many likely arise from a combination of genetic factors and some environmental influence. Once a provisional diagnosis of dystonia is made, elucidating the cause can be challenging, and a specific cause is not found in many cases. However, early diagnosis is important because some dystonias are treatable.

A modern definition for the dystonias

As a group, the dystonias are considered among the most poorly recognized of all of the movement disorders. Although a provisional diagnosis of dystonia can be made quickly by experienced clinicians, most patients report astonishingly long delays between symptom onset and diagnosis. A recent study of 146 consecutive patients with cervical dystonia seen at a tertiary care center in the USA revealed a mean time from symptom onset to diagnosis of 3.7 years (1). Another study of 107 consecutive patients with laryngeal dystonia reported a mean delay to diagnosis of 4.4 years (2). A recent Italian study revealed mean delays to diagnosis of 4.8 years for blepharospasm, 7.1 years for cervical dystonia, and 10.1 years for hand dystonias (3)*. These recent studies from the USA and Europe provide results that are similar to prior studies conducted in Australia and Canada (4). Moreover, a recent study addressing inter-rater reliability for diagnosis of various subtypes of dystonia among neurologists with different levels of training revealed surprisingly low levels of agreement (5)**. The long delays to diagnosis and poor diagnostic agreement among neurologists clearly demonstrate the need for better education, training and awareness of the dystonias.

There are many potential reasons contributing to the delays in diagnosis and poor diagnostic agreement. One factor is likely to be poor recognition of the many clinical manifestations of the dystonias, in part due to the inconsistent use of the term “dystonia”, even among experts. The definition of *dystonia* originated more than 100 years ago from Oppenheim’s description of several individuals who were hypotonic at rest, but became hypertonic with voluntary movement (6). Oppenheim coined the term *dys-tonia*, which means *abnormal muscle tone*, because he believed the essential defect involved neural regulation of muscle tone. Since then, many other clinical manifestations and subtypes of dystonia have been recognized, leading to drift in the definition and differences in expert opinion in different parts of the world. To develop international consensus, a panel of experts with broad expertise was assembled to establish a revised definition that more accurately captures modern views of all subtypes of dystonia:

> Dystonia is 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. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.

This revised definition was first published in 2013 after nearly 2 years of deliberation (7). Several subsequent commentaries have been published focusing on the rationale and clinical applications of these changes (8–10). The new definition places less emphasis on *hypotonia* as a core feature of dystonia. Hypotonia may occur, especially in certain inherited dystonias that emerge before 20 years of age, but it is infrequent in the more common focal and

segmental dystonias that emerge in adults. More emphasis was placed on the intermittent nature of dystonic movements, to address frequent clinical misconceptions that they are always sustained and twisting (11, 12). Some common examples of intermittent dystonic movements include eye blinks in blepharospasm, tremor-dominant dystonia, and myoclonic dystonia. Additional emphasis was given to the patterned quality of movements, to emphasize the stereotypical quality seen in the dystonias, and to differentiate them from the more random appearance of chorea. This modern consensus definition has been widely cited and, hopefully, will improve clinical recognition and diagnosis of the many varied clinical features of the dystonias.

A modern classification strategy for the dystonias

The consensus panel that revised the definition for dystonia (7, 8) also provided recommendations for modernizing our means of classifying the growing numbers of subtypes (Table 1). The new classification system has two main axes, each with subgroups. The first axis addresses the different clinical manifestations with four dimensions: body region affected, age at onset, temporal aspects, and any associated clinical manifestations. Classification by body region affected includes focal dystonia, segmental dystonia, multifocal dystonia, hemi-dystonia and generalized dystonia. The classification by age at onset is based on 5 age groups. Classification by temporal aspects includes manner of onset (acute or insidious), short-term variations in symptoms (diurnal, intermittent, action-induced), and longer-term variations in severity (static or progressive). Classification according to the presence or absence of associated features addresses whether dystonia occurs by itself (isolated dystonia, previously known as primary dystonia) or is part of a more complex syndrome that combines other features (combined dystonia, previously known as secondary dystonia or dystonia-plus).

These dimensions for the clinical classification were selected because they have clear relevance for diagnosis and treatment. The classification by age at onset has important implications for diagnosis, with different etiologies most likely occurring in specific age groups. In general, those with onset during adolescence or earlier are more likely to have an identifiable genetic etiology. In contrast, a cause usually cannot be found for those in whom onset occurs later in adulthood. The classification by temporal aspects also is relevant for diagnosis. For example, those with a progressive disorder are more likely to have an underlying degenerative disorder, while those with acute onset and non-progressive disorder raise concern for rapid-onset dystonia-parkinsonism or a conversion disorder. The classification by body region affected has implications for treatment, because those with focal and segmental patterns are most often best served by local injections of botulinum toxins, while those with broader patterns may require surgical interventions such as deep brain stimulation. Finally, classification according to associated clinical features has implications for clinical diagnosis of a large number of complex neurological disorders where dystonia may be present.

A separate axis was proposed for classifying the dystonias according to known etiology. This axis addresses evidence for whether the disorder is inherited or acquired, and whether

there is any associated neuropathology. Both of these issues are directly relevant for diagnosis and treatment.

Clinical implications of recent genetic advances in the isolated dystonia syndromes

Several genes responsible for isolated dystonias have now been identified. The *TOR1A* gene (DYT1) encodes torsinA, which is thought to function as a protein chaperone (13). It classically was associated with familial childhood onset limb dystonia that very often progressed to generalized dystonia within a few years. The *THAP1* gene encodes the Thanatos-associated protein domain containing apoptosis associated protein 1, which is a DNA transcription factor (14). It has been linked with familial adolescent-onset focal or segmental dystonia often involving the craniocervical regions and upper limbs, again with frequent generalization. Through the use of next generation sequencing, three additional genes have been described since 2012. The *CIZ1* gene (DYT23) encodes an enzyme involved in DNA replication and has been linked with familial cervical dystonia (15). The *ANO3* gene (DYT24) bears homology to a chloride channel and has been linked with familial tremor-dominant cervical dystonia (16). The *GNAL* gene (DYT25) encodes a G-protein involved in neuronal signaling linked with familial adult-onset craniocervical dystonia (17, 18).

Since the original descriptions of these genes and their associated dystonia phenotypes, several additional reports have appeared, with some general principles with clear clinical implications (19–29). First, each gene was originally identified as a cause for one or more rare familial dystonias, but each also may be responsible for sporadic cases. Thus, the lack of a family history does not rule out involvement of one of these genes. Second, several of the genes originally were associated with onset in childhood or adolescence, but most also have been associated with onset later in adulthood. Thus they must be considered in patients with onset at any age. Third, each gene has been associated with a much broader spectrum of clinical phenotypes than originally described, making it difficult to predict the responsible gene. Finally, large-scale screening studies for these genes among patients with various types of isolated dystonia have led to estimates that they collectively account for no more than 2% of all isolated dystonias. Consequently, clinical diagnostic testing for these genes provides a very low yield and is not generally recommended.

However, genetic testing is warranted when onset is early or there is a clear family history. In these cases, deciding which gene to target for testing is challenging because the spectra of clinical phenotypes overlap considerably. Enthusiasm for broad dystonia gene panels is low because the cost is high and the rapidly growing list of genes renders the results of a “complete panel” incomplete in a few years. An emerging approach to this challenge is whole exome or whole genome sequencing, which can now be conducted by many clinical diagnostic laboratories (30, 31**). This diagnostic test allows for the simultaneous assessment of multiple known causative genes and can aid in the identification of mutations where the clinical phenotype does not follow typical syndromic patterns. For example, patients with ataxia telangiectasia may have isolated dystonia rather than ataxia as the presenting or dominant clinical feature, and may first present as adults rather than in

childhood (32–35)**. These unusual cases can be readily identified as having mutations in the *ATM* gene by exome sequencing, but would not be picked up by most targeted dystonia gene panels. Finally, results from clinical gene sequencing can be stored and queried at a future date. This last aspect means that testing does not have to be repeated when new genetic mutations are discovered. Instead, the original test results can be re-examined to assess the potential contributions of the new gene. The transition from clinical diagnostic tests that rely on panels of selected genes to tests that utilize next generation sequencing has been steadily gaining ground for other neurological diseases over recent years (36–38)**, and provides an obvious approach for inherited dystonias too.

New diagnostic and treatment strategies for combined dystonia syndromes

For many years, no new medications with broad clinical utility across various forms of dystonia have emerged. The botulinum toxins continue to serve as the main therapy for most patients with focal and segmental dystonia (39–41), including both isolated or combined dystonia syndromes. Several safe and effective formulations are available in different parts of the world. Although no formal comparisons among the available brands have been published, the similarities are more striking than the differences. Deep brain stimulation also provides an effective option for patients with many isolated dystonia syndromes and some combined dystonia syndromes (42–44). New and improved devices continue to be developed, and strategies for patient selection and post-operative management are constantly being improved.

In addition to treatments such as botulinum toxins and deep brain stimulation that have broad efficacy across many types of dystonia, there are a few treatments that are highly effective in certain rare combined dystonia syndromes. Therefore, most experts recommend diagnostic algorithms to test for these few rare combined dystonia syndromes. One example is dopa-responsive dystonia, where levodopa can eliminate dystonia in most cases. Another example is Wilson’s disease, where copper-reducing therapies can prevent worsening and sometimes reverse dystonic movements (45–47). Thus diagnostic testing for both disorders should be considered in virtually all patients with dystonia, especially children and young adults. Both disorders should be considered even when the clinical syndrome occurs at an age later than expected or lacks some of the classical clinical features.

However, two recent publications suggest that the traditional strategies emphasizing a few “treatable” dystonias should be reconsidered. A systematic review of dystonias that first emerge in children and adolescents listed 35 different disorders where specific disease-related treatments are now available (48)**. Although this report focused on children and adolescents, many of the disorders listed occasionally may emerge later in adulthood, similar to dopa-responsive dystonia and Wilson’s disease. Another publication addressing current strategies for diagnosis and treatment listed 27 disorders with disease-specific treatments (45)*. Although all of the disorders listed in both reviews are rare, it is essential to avoid missing them because effective mechanism-specific treatments are now available to slow disease progression and sometimes reverse dystonic symptoms.

These articles point to the need to modify traditional diagnostic approaches that emphasize only dopa-responsive dystonia and Wilson's disease. While dystonia experts can readily recognize the many different syndromic patterns that point to the diagnosis of these rare disorders, general practitioners encounter these patients very infrequently, so a diagnostic strategy that requires syndromic pattern recognition may be challenging for clinicians who do not specialize in dystonia. Additionally, the list of treatable dystonias has been growing steadily in recent years because of our rapidly advancing knowledge of biological causes, and the development of interventions that target the relevant mechanisms. Keeping up with the rapidly changing list of treatable dystonias can be challenging, even for experts. Finally, even experts can be led astray by atypical clinical presentations, such as isolated dystonia appearing in an adult with ataxia telangiectasia as described above (32–35).

There are two potential approaches for identifying the infrequent but growing numbers of treatable dystonias. The traditional strategy involves delineating clinical syndromes that match known diseases, and then targeting diagnostic testing for these specific disorders. This approach is likely to continue to be used by experts who are familiar with the many syndromes, and especially for patients who present with classical clinical phenotypes. Whole exome sequencing provides another approach for diagnosing many of these cases (31). This strategy is likely to capture even atypical clinical syndromes, and may be easier to apply for clinicians who do not specialize in dystonia or neurogenetics. Most likely some combination of these two strategies will be most useful (48). Targeted diagnostic testing for one or a few disorders may be most appropriate for patients who present with readily recognizable and classical clinical syndromes, while the broader net of whole exome sequencing may be preferable for those who present with syndromes that do not point clearly to a specific disorder. Whole exome sequencing is likely to be increasingly used, because its cost has been steadily decreasing, and it is now less expensive than some targeted gene panels. It has already proven useful for other neurological disorders, such as ataxia (37, 49).

Conclusions

Our information on the varied clinical manifestations of the dystonias and their underlying causes has grown dramatically in recent years. This increase in information has led to the need to revise the core definition of this group of disorders and the manner in which we subclassify them. This new information has also led to increasing awareness that traditional diagnostic and treatment strategies must also change. Next generation sequencing has revolutionized our approach to understanding the genetic substrates for dystonia, and recent clinical applications in other disorders have made it clear that these methods are likely to have a critical impact on our core strategies for diagnosis and treatment of the dystonias.

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Key Points

- The new definition for the dystonias provides a more inclusive description of the many subtypes, and should aid in more rapid recognition and improved diagnosis.
- The new classification system for the dystonias provides a more clinically useful approach for diagnosis than previously used strategies.
- The many recent advances in the genetics of dystonia syndromes point to the need to shift away from traditional diagnostic methods that focus on one gene at a time to modern methods that comprehensively screen for many or all genetic variants.
- There is an increasing number of dystonias for which specific mechanism-based treatments are available; although most of them are rare, they are important to recognize because successful interventions are now available.

Table 1

Classification of the dystonias according to clinical and etiological features

Axis I: Clinical Features	Age at onset	Infancy (birth to 2 years)
		Childhood (3–12 years)
		Adolescence (13–20 years)
		Early adulthood (21–40 years)
		Late adulthood (40 years and older)
	Body distribution	Focal (one isolated body region)
		Segmental (2 or more contiguous regions)
		Multifocal (2 or more non-contiguous regions)
		Hemidystonia (half the body)
		Generalized (trunk plus 2 other sites)
	Temporal pattern	Disease course (static vs progressive)
		Short-term variation (persistent, action-specific, diurnal, paroxysmal)
	Associated features	Isolated (may include tremor)
		Combined (includes other neurological or systemic features)
Axis II: Etiology	Nervous system pathology	Degenerative
		Structural (focal lesions, degenerative changes, etc…)
		No degenerative or structural pathology
	Heritability	Inherited (autosomal dominant or recessive, sex-linked, mitochondrial)
		Acquired (brain damage, drugs/toxins, space-occupying lesions, vascular, etc…)
	Idiopathic	Sporadic
		Familial