Invited Review

Dystonia: A Review and Update

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Abstract—Dystonia is the third most common movement disorder, yet remains widely under-recognized. Dystonia may be a primary disorder or symptomatic of an additional underlying neurological condition. Accurate diagnosis and effective treatment for patients will rely on increased awareness and knowledge about dystonia. In this review, we summarize the history, epidemiology, and pathophysiology of dystonia, followed by a focus on clinical features and the new classification system. We then highlight evidence-based recommendations from clinical trials.

Keywords—dystonia, dystonic disorders, movement disorders.

I. INTRODUCTION AND DEFINITION

Dystonia is the third most common movement disorder, yet it is still a widely under-recognized disorder, particularly to medical practitioners outside of neurology. This may be partly due to the variability in its clinical presentation. The definition of dystonia was recently updated by an international panel of experts in a special issue of the Movement Disorders journal to reflect this heterogeneity.¹

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

This article summarizes the origins, clinical features, evaluation, and management of this complex disorder for the practicing clinician.

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II. HISTORY

The term dystonia was first introduced in a 1911 paper by Hermann Oppenheim, a preeminent German neurologist.² In the paper, he described a condition in four unrelated Jewish children from Russia and Galicia, in which tone was intermittently increased or decreased. The condition was further characterized by muscle spasms causing twisted postures of the limbs and trunk, including scoliosis and lordosis. The twisted postures worsened with walking, and at times resembled a dromedary. The condition was progressive and some postures became fixed over time.³ While he initially considered these patients to have either hysteria or bilateral athetosis, ultimately he decided this was a new disease and proposed the names dystonia musculorum deformans and dysbasia lordotica progressiva.²³

Oppenheim may have coined the term dystonia, but he was not the first to describe patients with this phenomenology. Marcus Walter Schwalbe, a psychiatry doctoral student, described three Jewish siblings from Lithuania with similar presentations in his thesis presentation. He referred to their condition as “maladie des tics and tonic cramps with hysterical symptoms.” In 1911, Schwalbe’s professor, Theodor Ziehan, published these cases as “torsion neurosis.”² Also in 1911, a third paper was published from Edward Flatau and Wladyslaw Sterling in Poland, describing a similar condition in two Jewish boys as “progressive torsion spasms”.²

Cases of what we now recognize as dystonia were described by the medical community as early as 1713, when a description of probable writer’s cramp was published.⁴⁵ Subsequent reports include a case dubbed “Scrivener’s palsy” in 1864⁶; descriptions of writer’s cramp by the British Civil Service in the 1830s⁷; cases of blepharospasm and oromandibular dystonia by Horatio Wood in 1887⁸; publication of “wry neck” photos in 1896⁹; and a case of “tetric chorea” in Wilson’s disease by William Gowers in 1888.¹⁰

In 1929, it was widely believed within the medical community that dystonia was a symptom of an underlying condition, rather than a unique disease.² This perspective was largely based on the growing number of cases of dystonia described as secondary to cerebral palsy, post-encephalitic parkinsonism, Wilson’s disease, Parkinson’s disease, and...
Huntington’s disease. However, in 1944, Dr. Ernst Herz, a German-American neurologist, described cases of isolated dystonia with an electromyographic signature of co-contraction of agonist and antagonist muscles. His cases as well as the unique electromyographic findings supported its existence as a primary disorder.\textsuperscript{2,10} Since this time there has been considerable growth in the understanding of the etiology and treatment of dystonia as a primary disease.

III. EPIDEMIOLOGY

In general, the prevalence of dystonia is likely underestimated due to under-diagnosis. Moreover, differences in study designs and populations yield highly variable estimates. The prevalence of primary early-onset dystonia in the Ashkenazi Jewish population in New York City has been proposed to range from 50 to 111 people per million.\textsuperscript{11} In northern England, the prevalence of primary late-onset dystonia is estimated to be 430 to 600 people per million.\textsuperscript{12} The Rochester Epidemiology Project found the United States incidence of primary early-onset dystonia to be 2 per million per year, and the incidence of late-onset dystonia to be 24 per million per year.\textsuperscript{13}

IV. CLINICAL FEATURES

The clinical features of dystonia are highly variable between individuals, and also intermittent within a single individual. To those unfamiliar with dystonia, the presentations can appear bizarre and raise suspicion of a functional etiology. Accurate diagnosis relies heavily on the medical provider’s familiarity with the range of clinical characteristics of dystonia.

While individual presentations of dystonia vary, as a disorder, dystonia has a number of common clinical features. Abnormal movements and postures are usually stereotyped, involving the repeated contractions of the same muscle groups. The postures are often sustained, though phasic movements and tremor are common. The dystonia is activated by voluntary movements, frequently worse with walking, and may even be task-specific. The presence of a sensory trick (“geste antagoniste”) is highly suggestive of dystonia.

In addition to motor abnormalities, mood disorders including anxiety, social phobia, and major depression are common in patients with dystonia, and may precede the onset of motor symptoms.\textsuperscript{14} The presence of these non-motor symptoms further misleads many clinicians to make the misdiagnosis of a functional movement disorder.

CLASSIFICATION

Over the last century, as knowledge of the characteristics and etiologies of dystonia has grown, classification systems have evolved to highlight these differences. The most recent classification scheme proposed in 2013 was developed to help detect clinical syndromic patterns to aid in ascertaining the underlying etiology.\textsuperscript{1} This scheme has two axes; the first is based on clinical characteristics and associated features, the second is focused on etiology.

Axis 1 classification includes the key clinical aspects of age of onset, body distribution, and temporal pattern. Categories for age of onset include infancy (0-2 years), childhood (3-12 years), adolescence (13-20 years), early adulthood (21-40 years), and late adulthood (over 40 years). Body distribution can be focal, segmental (two contiguous body regions), multifocal (more than one non-contiguous body region), generalized, or hemidystonia, the latter of which is usually secondary to an underlying neurological insult. The temporal pattern is specified in terms of disease course, whether static or progressive; and variability, which can be described as task-specific, diurnal, paroxysmal, or persistent. This axis also includes associated features to separate isolated (formerly “primary”) dystonia from dystonia combined with other movement disorders, neurological findings, or systemic manifestations.\textsuperscript{1}

Axis 2 is designed to provide classification by etiology.\textsuperscript{1} It takes into account pathology, inheritance, and potential underlying causal mechanisms. Often there is no obvious pathological finding in individuals with dystonia, but if present, these may include evidence of degeneration or structural lesions. A structural lesion is likely to cause a static course. Inheritance may be autosomal dominant, autosomal recessive, X-linked, or mitochondrial. If no family history is present, dystonia is considered sporadic. Reported cases of acquired dystonias include lesions due to brain injury, infection, toxins, drugs, vascular abnormalities, paraneoplastic syndromes, or functional origin.

It is important to mention that another commonly used classification for inherited dystonias is the DYTn coding system developed by the Human Genome Organization Gene Nomenclature Committee. Several problematic features of this system prompted the development of the new 2013 classification system. These problematic features include the following: many DYTn designations were made as “placeholders” before the actual gene loci abnormalities were identified; the genes included are both risk factors and causative mutations; some DYTn designations are limited to single families or have later been found to have erroneous linkage; the list incorrectly suggests that the disorders are of the same phenotype and primarily dystonic in nature; the classification system is incomplete with both missing inherited dystonias and missing loci.\textsuperscript{1,15} Despite these concerns with the DYTn coding system, the DYT descriptions are widely used in dystonia nosology and we will include these in the descriptions of selected dystonias below.

SELECTED DYSTONIAS AND DIAGNOSTIC EVALUATION

The four cases Oppenheim originally described in his paper are cases of what we now call early-onset generalized isolated dystonia (Videos 1-3). The first identified genetic cause of early-onset generalized dystonia is DYT1, caused by a mutation in the gene encoding Torsin 1A. The most common
<table>
<thead>
<tr>
<th>Focal dystonias</th>
<th>Clinical features</th>
<th>Misdiagnoses</th>
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<tbody>
<tr>
<td>Blepharospasm</td>
<td>Increased blink frequency, forced eye closure</td>
<td>Tics, dry eyes, myasthenia gravis</td>
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<tr>
<td>Oromandibular dystonia</td>
<td>Jaw opening, closing, or deviation; tongue, platysma, and lip involvement common; may be associated with cervical dystonia or blepharospasm</td>
<td>Temporomandibular joint disorders, dental problems</td>
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<tr>
<td>Spasmodic dysphonia</td>
<td>Tight, strangled, whispery voice</td>
<td>Laryngitis, strain, functional</td>
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<td>Musician’s dystonia</td>
<td>Task-specific to instrument, most often focal hand or embouchure, depending on instrument; 1 in 200 professional musicians; 4:1 males to females</td>
<td>Cramps, fatigue, peripheral neuropathy</td>
</tr>
<tr>
<td>Writer’s cramp</td>
<td>Task-specific to writing</td>
<td>Cramps, fatigue, peripheral neuropathy</td>
</tr>
<tr>
<td>Inversion dystonia (runner’s dystonia)</td>
<td>Foot inversion and plantar flexion; task specific to walking or running</td>
<td>Foot drop, arthritis</td>
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<td>The yips (in athletes, classically golfers)</td>
<td>Focal hand dystonia resulting in loss of dexterity and coordination and decline in athletic performance</td>
<td>Anxiety</td>
</tr>
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</table>

Table 1: Examples of focal dystonias, clinical characteristics, and common misdiagnoses

mutation in this gene, \textit{TOR1A}, is a three base pair deletion in the coding region. This specific mutation is found in 90\% of Ashkenazi Jewish cases, and in 60\% of non-Jewish cases.\textsuperscript{16} Although this is a dominant mutation, penetrance is roughly only 30\%.\textsuperscript{17} Typically the initial onset involves a limb and occurs prior to the age of 26. Over time, the dystonia generalizes, but often spares cranial muscles. In adults, there may be limited spread, resulting in only focal limb involvement.

\textit{DYT6} dystonia is another autosomal dominant disorder with reduced penetrance. It is associated with a \textit{THAP1} gene mutation, first reported in Amish-Mennonite families, but is now known to be more widespread. Typically it causes adolescent or adulthood onset of cranio-cervical or upper-limb dystonia, which occasionally goes on to generalize.

Segawa’s disease, \textit{DYT5}, is one of the Dopa Responsive Dystonias (DRDs). These dystonias are due to a deficiency within the dopamine synthesis pathway. The most salient clinical features of DRDs are diurnal fluctuations and a robust response to levodopa. Most often \textit{DYT5} has childhood onset, affecting females more than males. There is variable expression, as it may also present as a gait disorder or developmental delay. In adults, it presents as a focal or multifocal dystonia, or parkinsonism.

Dystonia in children is commonly misdiagnosed as scoliosis, cerebral palsy, or a functional movement disorder. The recommended diagnostic evaluation in children is genetic testing for the \textit{DYT1 (TOR1A)} and \textit{DYT6 (THAP1)} mutations, a levodopa trial to determine presence of a DRD, copper studies to rule out Wilson’s disease, brain imaging, and metabolic studies to look for other neurological or systemic diseases, particularly if there are any additional findings on physical exam.

Adult-onset focal dystonias most often occur in early or late adulthood. They can be focal or segmental, persistent or paroxysmal, and sporadic or familial. Of the few known autosomal dominant genetic mutations linked to adult-onset focal dystonia, the penetrance is estimated to be 12-15\%,\textsuperscript{18} which may cloud the inheritance pattern and thereby appear sporadic. Cervical dystonia is the most common manifestation of adult-onset focal dystonia (video 4). It can appear to have a fairly abrupt onset, and is not typically progressive. Neck pain is present in 75\% of patients.\textsuperscript{19} Sensory tricks are present in over 50\% of patients.\textsuperscript{20} About 10\% of cases remit spontaneously, but the majority recur.\textsuperscript{19} There is a 2:1 female to male ratio, with a peak age of onset of 40-50 years. The abnormal head posture may consist of lateral rotation (turn, or torticollis), tilt (laterocollis), neck flexion (anterocollis) or extension (retrocollis), lateral shift, sagittal shift, or shoulder elevation. Tremulous or jerky phasic movements often accompany tonic abnormal posture. Typically, there is visible or palpable local muscle hypertrophy of the sternocleidomastoid and posterior neck musculature. Common misdiagnoses in cervical dystonia include osteoarthritis, disc herniation, neck strain, essential tremor, and functional origin.
It is important to identify non-dystonic causes of torticollis, though rare, as these include potentially malignant etiologies. Non-dystonic torticollis can result from orthopedic injuries, congenital muscular torticollis, cervical cord tumors, posterior fossa tumors, neck or pharyngeal abscesses, and trauma. Diagnostic clues to these non-dystonic causes include the lack of a sensory trick, fixed neck and shoulder postures, lack of involuntary movements, persistence in sleep, and antecedent trauma.

Other types of focal dystonias are listed in Table 1 and include blepharospasm (video 5), writer’s cramp, and inversion dystonia (videos 2 and 3, respectively, in a case of generalized dystonia). The evaluation of new adult-onset focal dystonia must include a thorough neurological exam, particularly looking for signs of parkinsonism, as idiopathic Parkinson’s disease can present with dystonia or develop it later in the disease course (videos 5 and 6). Additional investigations should include brain imaging; cervical imaging for torticollis with atypical features, particularly if it is of acute onset or fixed posture; copper studies to rule out Wilson’s disease; and a levodopa trial for DRD, particularly for multifocal dystonias.

Acquired dystonias, also referred to as secondary dystonias, may be suspected in cases of hemidystonia, fixed postures, abnormal head imaging, history of brain injury, or the presence of other neurological findings. Table 2 lists possible etiologies of acquired dystonias.

### V. PATHOPHYSIOLOGY

Physiological studies that seek to identify the basis for dystonia have been hindered by difficulty in differentiating which physiologic features are causal versus secondary. The principle pathophysiological components are reduced intracortical inhibition, sensory dysfunction, and abnormal synaptic plasticity.21 There is evidence from studies utilizing several different modalities of reduced inhibition in the spinal cord, brainstem, and cerebral cortex, supporting the hypothesis that the disrupted surround inhibition results in overflow activation and loss of selectivity.21 The sensory dysfunction in dystonia includes sensory alterations preceding symptom onset, and loss of sensory spatial and temporal discrimination. Synaptic plasticity in dystonia is altered, disrupting homeostasis. This leads to facilitation of synaptic potentiation and loss of inhibitory processes.21 Currently, it is thought that these changes in the sensorimotor system lead to the development of dystonic movements.

### VI. MANAGEMENT

Treatment for dystonia consists of medications, chemodenervation, and surgical therapies. Dopa-responsive dystonia responds well to low doses of dopaminergic therapy. Other pharmacological treatments for dystonia do not target specific deficient biological pathways and their efficacy is less predictable.

<table>
<thead>
<tr>
<th>Acquired causes of dystonia</th>
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<tr>
<td>Perinatal brain injury</td>
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<td>Demyelinating disease</td>
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<td>Head trauma</td>
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<td>Encephalitis</td>
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<td>Peripheral trauma</td>
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<td>Pontine myelinolysis</td>
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<td>Stroke</td>
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<td>Cardiolipin antibodies</td>
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<td>Tumor</td>
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<td>Drug-induced</td>
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Trihexyphenidyl is one of the most studied medications in dystonia. It is often used in the treatment of generalized dystonia, and is particularly better tolerated in children.23,24 In a double-blind crossover study of 31 patients with primary dystonia, trihexyphenidyl provided a clinically significant improvement of symptoms in 71% of patients.23 Use of trihexyphenidyl is often limited in adults due to cognitive dulling and other anticholinergic side effects.

Dopamine receptor blockers may cause cognitive dulling, tardive dyskinesias, and other side effects, limiting their efficacy in dystonia. Of these, clozapine, an atypical neuroleptic, has less risk of tardive dyskinesia, and has improved tardive dystonia symptoms in 5 out of 5 patients in an open label trial, although treatment was limited by side effects and the need for monitoring, resulting in the discontinuation of therapy in 3 of these 5 patients.24 Tetrabenazine is a reversible pre-synaptic monoamine depleter that can be beneficial especially for tardive dystonia.25

Other medications often used to treat dystonia, largely based on empiric evidence, include muscle relaxants and benzodiazepines. Of these, baclofen is recommended as the most effective.22 Intrathecal baclofen has been shown to provide symptom improvement in patients with medication-refractory generalized dystonia in a cohort of 86 patients, 71% of whom had dystonia associated with cerebral palsy.26

Chemodenervation with botulinum toxin injections is now the most highly recommended treatment in focal and segmental dystonia given its high efficacy and low rate of systemic side effects. There have been a few double-blinded, placebo-controlled studies showing the efficacy of botulinum toxin injections in cervical dystonia.27,28 It is also effective for other focal dystonias, including focal hand dystonia and adductor spasmodic dysphonia.29,30 The primary potential side effect of concern from botulinum toxin injections is temporary excessive muscle weakness in the muscles injected or adjacent muscles due to medication spread. Depending on the area injected, this muscle weakness may cause...
dysphagia, ptosis, or impaired limb use until the effects of the botulinum toxin wear off.

Deep brain stimulation (DBS) can be effective in decreasing dystonia symptoms and improving quality of life in medication-refractory generalized dystonia. In primary generalized DYT1 dystonia, shorter disease duration at the time of surgery is associated with better long-term DBS outcomes. There have been increasing reports of efficacy of DBS for cervical dystonia. A recent randomized sham-controlled trial showed efficacy of pallidal DBS in improving cervical dystonia symptoms in patients with sub-optimal response to botulinum toxin injections. Pallidal DBS can also be of benefit in medication-refractory tardive dystonia. Comprehensive reviews of DBS for dystonia have been recently published by Vidalhiet et al. and Mills et al. Currently, there is not enough evidence of efficacy of paramedical therapies such as physical therapy, speech therapy, sensorimotor training, or transcutaneous electrical nerve stimulation (TENS) to recommend these as treatments for dystonia.

VII. CONCLUSIONS

Dystonia is a common movement disorder with variable presentations that is often unrecognized and under-diagnosed. In the past century, there have been tremendous advances in understanding the pathology and genetics of dystonia, which has led to improvements in diagnosis and classification. Individuals with dystonia will benefit from continued improvements in clinical recognition, diagnosis, and treatment.

APPENDIX

Video captions:

This patient’s dystonia started in childhood; genetic testing for known causes of generalized dystonia have been negative. This video demonstrates prominent cranio cervical dystonia, including jaw closure, grimacing, blepharospasm, right laterocollis, right torticollis, left lateral shift, posterior sagittal shift, anterocollis (downward deviation of the chin), all increased with activation, especially speech. Speech reveals dystonic tongue movements and spasmodic dysphonia This video also demonstrates mild dystonic posturing of the left arm and associated hypokinesia and decrement of rapid alternating movements, left greater than right.

Video 2: Patient 1. Writer’s cramp due to generalized dystonia.
Dystonic posturing of the right hand is seen while writing, characterized primarily by wrist extension, with associated finger flexion that may be dystonic or compensatory.

Video 3: Patient 1. Foot inversion dystonia due to generalized dystonia.
This video demonstrates inversion of both feet, left greater than right, as well as left greater than right, dystonic posturing of the hands while walking. The foot inversion is task-specific, as it is seen while walking but not in the previous videos while at rest or performing rapid alternating movements.

This patient’s cervical dystonia is characterized by left torticollis, right laterocollis, and limited range of motion of right head turn with associated irregular, jerky dystonic head tremor. Right sternocleidomastoid hypertrophy is visible, best seen in this video while patient is turning to the left. Left head turn reaches a null point, at which the patient no longer has any involuntary muscle contraction.

This patient has dystonia affecting her eyes and limbs associated with Parkinson’s disease. This video features blepharospasm, dystonia causing involuntary eyelid closure. She demonstrates how a sensory trick of touching and pulling on the skin below her eyes allows her eyes to open.

This video demonstrates mild right foot plantar flexion and inversion, with compensatory toe extension. As the patient walks, she develops a dromedary gait, particularly in the right leg, with right hip and knee flexion during the swing phase. Both hands are held in a dystonic posture, fisted with thumb extension.

References