The Dystonias

H. A. Jinnah, M.D., Ph.D., and Tyler Reimschisel, M.D.

Dystonia is a neurologic disorder with an extremely broad range of clinical manifestations that may emerge at any age. The basic underlying problem involves overactivity of the primary muscles responsible for voluntary movement, overflow activation of extraneous muscles that are not normally required for a specific movement, and coactivation of muscles that simultaneously antagonize the action of the primary muscles. The net outcome is determined by the severity and distribution of muscles involved. In some cases dystonic movements may manifest merely as transient exaggerations of a normal movement. In other cases dystonic movements take on a quality that is slow, stiff, cramped, twisting, or jerky. In extreme cases dystonia is associated with the development of odd postures that may become progressively bizarre or lead to fixed deformities. Unlike chorea or athetosis, the movements of dystonia tend to be patterned or stereotyped in individual cases.

Classification

Classification of the many types of dystonia into specific subgroups is important because of implications for treatment and prognosis. The dystonias can be differentiated by a number of features, including the areas that are affected, the age of onset, temporal aspects, and etiology. The classification by areas affected is shown in Table 1. *Focal dystonia* describes cases with involvement of isolated areas, such as one hand in writer's cramp or the periocular muscles in blepharospasm. *Segmental dystonia* describes cases with involvement of multiple contiguous areas, and *multifocal dystonia* describes those with involvement of multiple noncontiguous areas. *Generalized dystonia* describes cases with broad involvement, although specific areas in individual cases are typically more affected than others.

Classification by age of onset is also valuable because those with young-onset disease (<30 years) are more likely to have a discoverable inherited condition that often evolves into a generalized form, whereas those with adult-onset disease (>40 years) are more likely to have a relatively static or focal problem without discoverable cause. Dystonia also can be described by temporal aspects, including manner of onset and progression, short-term fluctuations such as diurnal variability or occurrence in discrete attacks, or type and duration of activity that induces dystonia such as writing or walking.

Finally, the dystonias may be classified by known or suspected etiology. As shown in Table 2, dystonia has been associated with virtually all known processes that can influence the nervous system, including stroke, space-occupying lesions, toxic/metabolic insults, and inflammatory processes. It is a regular feature of many developmental and degenerative diseases. Dystonia may also occur in the absence of any associated neurologic abnormalities or disease process, in which case it is referred to as *primary* or *idiopathic torsion dystonia*.

Diagnosis

CLINICAL EVALUATION

Because of the broad range of clinical manifestations and underlying causes, it is difficult to develop universal algorithms for evaluation of all cases of dystonia. The diagnosis relies heavily on a careful clinical evaluation. Important historic features include age at onset,

TABLE 1 Classification Based on Affected Region

- Focal dystonia (isolated region)
  - Blepharospasm (periocular muscles only)
  - Oromandibular (jaw, tongue, or perioral)
  - Laryngeal (spasmodic dysphonia)
  - Cervical (torticollis, retrocollis)
  - One limb (writer's cramp, foot dystonia)
- Segmental dystonia (two contiguous regions)
  - Meige's syndrome (blepharospasm + oromandibular dystonia)
  - Cervical dystonia + one arm
- Multifocal dystonia
  - Hemidystonia (ipsilateral arm and leg)
  - Diffuse (two or more noncontiguous body areas)
- Generalized (more extensive areas)
  - Both legs, another region, ± trunk
  - One leg, another region, + trunk

TABLE 2 Classification Based on Etiology

- Primary (relatively isolated dystonia)
  - Inherited: early and adult onset, generalized or focal
  - Idiopathic: torticollis, blepharospasm, spasmodic dysphonia, and so forth
- Dystonia plus syndromes (prominent dystonia with other telltale features)
  - Dystonia/parkinsonism: DOPA-responsive, dopamine agonist responsive, rapid-onset dystonia/myoclonus
- Secondary (known environmental cause)
  - Perinatal injury: hypoxia/ischemia, kernicterus
  - Infectious/inflammatory: viral, bacterial, fungal, tuberculous, prion related
  - Autoimmune/paraimmune: demyelination, lupus, anticardiolipin, Reye's syndrome, subacute sclerosing panencephalitis
  - Trauma: brain, spinal cord, peripheral nerves
  - Neoplasm: direct effect or paraneoplastic
  - Vascular: ischemic stroke, hemorrhagic stroke, vessel malformations
  - Drugs: dopamine related, SSRI, anticonvulsants, cocaine, MPTP, ergots
  - Toxins: cyanide, manganese, carbon monoxide, carbon disulfide, disulfiram, methanol, 3-nitropropionic acid
  - Other: hypoparathyroidism, central pontine myelinolysis, cervical stenosis, congenital
- Hereditary/degenerative (recognized syndrome with or without known cause)
  - Parkinsonian: Idiopathic Parkinson's disease, corticobasal degeneration, progressive supranuclear palsy, multisystem atrophy
  - Trinucleotide repeat diseases: Huntington's disease, Machado-Joseph disease and other spinocerebellar ataxias, dentatorubral pallidal luysian atrophy
  - Lysosomal: metachromatic leukodystrophy, GM$_1$ and GM$_2$ gangliosidosis, Niemann-Pick C, Krabbe's disease, ceroid lipofuscinosis
  - Amino acidurias: homocystinuria, Hartnup's disease
  - Organic acidurias: glutaric aciduria 1, methylmalonic aciduria
  - Mitochondrial: Leigh's and Leber's diseases, dystonia/deafness syndrome
  - Metal/mineral metabolism: Wilson's disease, Hallervorden-Spatz disease, Fahr's disease
  - DNA handling: ataxia-telangiectasia, Cockayne's syndrome, xeroderma pigmentosa, Rett's syndrome
  - Miscellaneous: Lesch-Nyhan disease, Pelizaeus-Merzbacher disease, neuroacanthocytosis, adult and infantile striatal necrosis

DOPA, Dopamine; *SSRI*, selective serotonin reuptake inhibitor; *MPTP*, methylphenyltetrahydropyridine.

manner of progression, potential inciting events such as toxin exposures or trauma, and whether other family members are affected. Particularly close attention must be directed toward medications, because there is a long list of agents that can cause both acute dystonic reactions and tardive syndromes with prominent dystonia. The physical examination focuses on the body parts affected and whether or not there are associated findings that might point to a specific syndrome or identifiable cause.

COMMON DIAGNOSTIC TESTS

A thorough clinical evaluation provides an important guide for selecting among some of the commonly employed tests of neurologic function. Magnetic resonance (MR) imaging of the brain is warranted in virtually all cases, because it can uncover focal abnormalities underlying dystonia in some cases, or it can provide clues toward a developmental or degenerative process. Routine electromyographic (EMG) studies are generally not needed, unless there is suspicion for a neuromuscular cause of abnormal movements that may resemble dystonia, such as stiff person syndrome, tetany, or neuromyotonia. Multielectrode EMG can provide important confirmatory evidence for overflow activation or coactivation of antagonistic muscles when the clinical manifestations do not allow for an unequivocal diagnosis. Electroencephalography (EEG) is not generally needed, unless there is reason to suspect an associated seizure disorder or the dystonia comes in discrete attacks as in the paroxysmal dyskinesias.

ADDITIONAL DIAGNOSTIC TESTS

A thorough clinical evaluation is even more valuable for guiding a judicious selection of more specific tests, since it is not useful to perform a complete battery of tests covering all potential causes in all cases. When considering the need for further tests, it is helpful to divide patients into two groups based on the age at which dystonia first emerged.

For older patients (>40 years), the usefulness of additional testing depends on the type of dystonia. Aside from brain MR imaging, extensive testing is rarely revealing for the primary focal dystonias, such as blepharospasm, cervical dystonia, or writer's cramp. Additional testing is also of limited value when the clinical evaluation suggests that dystonia is part of a neurodegenerative syndrome such as corticobasal degeneration or progressive supranuclear palsy. Virtually all inherited developmental disorders may rarely present in adulthood. However, the yield for testing for most of these is very low and generally not necessary, unless the clinical features or family history point in a specific direction. Additional tests are therefore warranted only when the clinical evaluation suggests the dystonia might be related to some other identifiable process.

For younger patients (<40 years), additional tests are almost always warranted, especially if the condition is progressive or if there are associated neurologic features that point to a known hereditary cause. Organizing a complete work-up is a formidable task because of the long list of potential diagnostic tests. Rather than performing all the tests, it can be helpful to divide the tests into two groups. The first group of tests is mandatory and should be conducted in all patients without delay. They include tests for all potentially reversible disorders such as Wilson's disease, autoimmune disease, glutaric aciduria, and vitamin E deficiency. Although most of these disorders are quite rare, testing for them is important because dystonia can be prevented or reversed if the diagnosis is made early.

The second group of tests is much broader and should be considered optional. Although some authorities recommend performing a complete battery of tests covering the additional disorders listed in Table 2, we prefer a more targeted approach that is guided by the results of the clinical evaluation and neuroimaging. For example, disturbances of ocular motility might point to a mitochondrial defect or Niemann-Pick disease. Similarly, abnormalities on MR imaging can point toward a leukodystrophy or Hallervorden-Spatz disease. Because of limited familiarity with most of these rare diseases, consultation with an expert in neurogenetics can facilitate the selection of the most appropriate tests for each case. If there are no associated clinical or neuroimaging features to guide testing, then testing for mutations in the *DYT1* gene, the most common of the primary torsion dystonias, is warranted.

The decision to proceed with the second group of tests is a matter of personal preference that depends on a number of factors. Further testing is warranted for counseling of other potentially affected family members or carriers and can also be useful for providing information on prognosis and the natural history of the disease. Further testing is also warranted if a definitive diagnosis would provide closure for family members who will otherwise continue for years to seek answers. However, enthusiasm for further testing must be tempered by the large number of potential tests, the risks and discomforts associated with some tests (e.g., biopsy), the recognition that a positive test result will likely point to a disorder without a specific treatment, and the realization that a substantial proportion of cases remain undiagnosed despite exhaustive testing. The decision to proceed with further tests is often a difficult one, especially when a young child is involved. If there is any uncertainty, it can be useful to offer the "test of time" as an alternative, since making a diagnosis will not significantly alter the outcome in the many conditions for which no specific treatments are available. The evolution of symptoms and signs in many patients with early-onset dystonia may make one underlying cause more likely, facilitating a more focused approach to additional testing.

Treatment

GENERAL APPROACH

Because of the broad range of clinical manifestations and underlying causes, it is difficult to devise a universal algorithm appropriate for the management of all cases. Most specialists approach treatment in different ways for the many subclasses of dystonia. If a recognized cause is identified, specific treatments may be available to influence the underlying pathogenesis, such as copper-depleting therapies for Wilson's disease. The following sections are a summary of the most common options for symptomatic treatment, which must be tailored to individual needs.

COUNSELING

The best patient is an educated patient, so treatment in virtually all cases begins with counseling. Many people with dystonia, particularly the less common forms, go misdiagnosed for many years or are under the impression that they are suffering from a psychiatric or psychologic ailment. Some become extremely frustrated and frankly depressed. Education allows patients to begin the process of accepting the known realities of the disorder, learning from others, seeking help from local support groups, and keeping up with new trends via online resources.

Because patients are often not diagnosed for many years and pursue multiple treatments without benefit, many adopt a fatalistic view that nothing can be done to help. Providing education concerning the many available treatment options helps restore hope and alleviates this fatalistic view. In addition to restoring hope, it is important to provide realistic expectations for the efficacy of each treatment modality and the known risks. The difficult combination of hope with realistic expectations is a key starting ingredient for any satisfactory treatment program.

PHYSICAL AND OCCUPATIONAL THERAPY

An initial consultation with a physical or occupational therapist can be valuable in many cases to mobilize frozen joints, limit mounting contractures, offer education concerning appropriate exercise programs, and provide assistive devices for those who need them. Although regular treatments by a physical therapist probably do not alter the long-term course of the condition, many patients seem to benefit from return visits when things seem to be going in the wrong direction.

MEDICATIONS

Successful treatment of dystonia has been reported for an enormous array of medications, but only a few are sufficiently consistent to warrant serious consideration. With a few rare exceptions, none of the medications is dramatically effective, and all have substantial side effects. Despite these caveats, many patients opt to continue one or more to "take the edge off" the condition.

Dopamine-Related Medications

All children with dystonia deserve a trial of levodopa therapy, because it can nearly entirely eliminate motor disability in DOPA-responsive dystonia. Though such cases classically present with diurnal fluctuations in disease severity, all children with dystonia should be treated because relatively fixed or progressive presentations also occur. All adults with limb dystonia similarly deserve a trial of levodopa, because focal limb dystonia can be the presenting manifestation of Parkinson's disease. Start with one tablet of carbidopa/levodopa 25/100 daily and increase by one tablet every 3 to 5 days. Most children with DOPA-responsive dystonia respond to very low doses, but some require higher doses. An adequate trial for adults requires 1200 mg of levodopa daily (20 mg/kg in children) for at least 1 month.

Paradoxically, dopamine receptor antagonists have also been reported to be effective in the treatment of some forms of dystonia. However, they can also provoke

tardive movement disorder syndromes. The most common is tardive dyskinesia, but a syndrome with predominantly axial dystonia known as *tardive dystonia* may also occur. These developments may then unnecessarily complicate the clinical picture, so dopamine antagonists cannot be enthusiastically endorsed for most cases.

Trihexyphenidyl and Related Anticholinergics

Trihexyphenidyl has proven efficacy in many types of dystonia, although the benefits may not be dramatic and side effects are often limiting. Treatment begins with 1 mg daily and is increased by 1 mg every 3 to 5 days over a period of 1 month to a total dose of 2 mg three times a day. It may then be increased by 2-mg increments every week until side effects emerge or a dose of 30 mg three times a day is reached. It is worth noting that benefits may not occur until reaching 60 to 100 mg daily, well above the usual recommended doses. Young patients tolerate these extreme doses surprisingly well, although older patients do not. Patients should be warned about common side effects such as cognitive impairment, sedation, blurry vision, dry mouth, constipation, exacerbation of narrow-angle glaucoma, and heat intolerance.

Clonazepam and Related Benzodiazepines

Clonazepam also can be helpful for a variety of the dystonias, but again the benefits are often not dramatic, and there are concerning side effects. Start with a dose of 0.5 mg daily and increase by 0.5 mg every 3 to 5 days to a maximum dose of 2 mg three times a day. Patients should continue on the minimal doses required for benefits. They should be warned about side effects of cognitive impairment, sedation, impaired coordination, and negative interactions with alcohol. The potential for physical and psychologic dependence must be discussed explicitly, as well as the potential dangers of sudden discontinuation.

Baclofen

Another commonly used drug with some efficacy in several types of dystonia is baclofen. Start at 5 mg daily and increase by 5 mg every 3 to 5 days to a maximum dose of 30 mg four times a day. Warn patients about potential cognitive impairment, sedation, gastrointestinal upset, and impaired coordination. Abrupt discontinuation should also be discouraged, particularly at high doses.

BOTULINUM TOXINS

Local injections of botulinum toxins are extraordinarily effective for many dystonias and other disorders associated with excessive muscle activity. This treatment modality is most commonly considered for the treatment of focal and segmental dystonias, because of the technical difficulties associated with delivering the medication to patients with more widespread involvement. Two preparations are currently available: Botox and Myobloc. The details of their use are not further addressed here, because there are excellent chapters in this volume, several books devoted to their use, and instructional seminars yearly.

Although botulinum toxins are more commonly used in the treatment of the focal and segmental dystonias, they can also be extremely valuable in generalized dystonia, where they are often underutilized. The goal of treatment is not to treat all involved muscles but rather to target those areas that cause the most discomfort. For example, it is not unusual for cervical dystonia to be the most prominent and disabling element for some patients with generalized dystonia. Treatment of the cervical dystonia with botulinum toxin alleviates a primary source for discomfort and reduces the risk for acquired myelopathy.

SURGICAL PROCEDURES

A number of surgical procedures have been developed for specific types of dystonia. The surgical procedures are usually reserved for those cases with severely disabling or discomforting dystonia where less invasive therapies, such as oral medications and injection of botulinum toxins, have proven unsatisfactory.

Intrathecal Baclofen

Some patients experience remarkable improvements with continuous delivery of baclofen into the cerebrospinal fluid via a chronically implanted pump. The most significant improvements have been reported for patients with dystonia and spasticity of the legs, such as those with cerebral palsy. However, improvements are not limited to this population. This approach for the treatment of dystonia is probably underutilized, largely as a consequence of uncertainties regarding the best candidates, the limited numbers of centers with adequate experience with the technique, and the small but definite risks. Nevertheless, it is worth considering when other options have provided inadequate responses.

Selective Denervation for Cervical Dystonia

The use of botulinum toxins and oral medications provide the first line of therapy for most patients with cervical dystonia, but destruction of nerves innervating select cervical muscles offers a useful alternative for patients who do not respond to these modalities. This procedure probably also is underutilized as a consequence of the limited numbers of centers with adequate experience and the known side effects and risks. However, it can again be valuable for selected patients where the less invasive approaches have proved unworkable.

Functional Neurosurgery

Focused lesions of specific structures of the brain have also been employed as a treatment for dystonia. More recently, the lesion approach has been replaced by deep brain stimulation. Two consistent phenomena have been observed among the centers offering deep brain

stimulation for dystonia. First, improvements are often delayed by months after the procedure. Second, there is marked individual variability in responses. Some cases respond dramatically, whereas others show no effect. Some of the variability is related to the site selected for stimulation, with the pallidum and thalamus emerging as good targets. Perhaps a more important source of variability is the type of dystonia. In general the primary torsion dystonias seem to respond better than dystonias secondary to a known insult, though some benefits have been reported for most types.

The Activa stimulator is approved under the U.S. Food and Drug Administration Humanitarian Device Exemption for use in primary torsion dystonias by centers with approval by an Institutional Review Board. The procedure is not widely used because of limited experience selecting the best responding cases, the need for intraoperative electrophysiologic measurements to guide precise placement of the stimulator, the risks of surgery, and the need for ongoing management of the stimulator. However, it can be the only effective means of managing severe dystonia in selected cases.

ALTERNATIVE MEDICINE

Because of the limitations of traditional medical and surgical therapies, more than half of dystonia patients admit to seeking nontraditional remedies such as massage, acupuncture, chiropractic manipulations, herbal and dietary supplements, biofeedback, and others. Discouraging such trials does nothing for the physician-patient relationship, unless the approach is known to be counterproductive or dangerous. Instead, it is more useful to view such trials with an open mind. At the same time, it is important to explicitly inform patients that these alternatives are only rarely covered by medical insurance. Patients must be reminded regularly to critically re-evaluate whether the costs outweigh any benefits.

Summary

Dystonia is a neurologic disorder with a broad range of clinical manifestations and underlying causes. There are many options for treatment of the dystonias. In some cases, the treatments are dramatically effective and almost curative. In others, improvements are more modest. Virtually all patients with dystonia can enjoy some improvement in their quality of life if treatments are tailored to individual needs.

SUGGESTED READING

Fahn S, Hallett M, Delong MR: Dystonia, *Adv Neurol* 94:4, 2004.

PATIENT RESOURCES

Dystonia Medical Research Foundation
1 East Wacker Drive, Suite 2430
Chicago IL, 60601
http://www.dystonia-foundation.org/

WE MOVE
204 West 84th Street
New York NY, 10024
http://www.wemove.org/

National Spasmodic Torticollis Association
9920 Talbert Avenue
Fountain Valley CA, 92708
http://www.torticollis.org/