

The Dystonias



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What are the dystonias?


The dystonias are movement disorders in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures. The movements, which are involuntary and sometimes painful, may affect a single muscle; a group of muscles such as those in the arms, legs, or neck; or the entire body. Those with dystonia usually have normal intelligence and no associated psychiatric disorders.

What are the symptoms?

Dytonia can affect many different parts of the body. Early symptoms may include a deterioration in handwriting after writing several lines, foot cramps, and/or a tendency of one foot to pull up or drag; this may occur “out of the blue” or may occur after running or walking some distance. The neck may turn or pull involuntarily, especially when the patient is tired or stressed. Sometimes both eyes will blink rapidly and uncontrollably, rendering a person functionally blind. Other possible symptoms are tremor and voice or speech difficulties. The initial symptoms can be very mild and may be noticeable only after prolonged exertion, stress, or fatigue. Over a period of time, the symptoms may become more noticeable and widespread and be

unrelenting; sometimes, however, there is little or no progression.

How are the dystonias classified?

 One way to classify the dystonias is according to the parts of the body they affect:

- *Generalized dystonia* affects most or all of the body.
- *Focal dystonia* is localized to a specific part of the body.
- *Multifocal dystonia* involves two or more unrelated body parts.
- *Segmental dystonia* affects two or more adjacent parts of the body.
- *Hemidystonia* involves the arm and leg on the same side of the body.

Some patterns of dystonia are defined as specific syndromes: *Torsion dystonia*, previously called *dystonia musculorum deformans* or **DMD**, is a rare, generalized dystonia that may be inherited, usually begins in childhood, and becomes progressively worse. It can leave individuals seriously disabled and confined to a wheelchair. Genetic studies have revealed an underlying cause in many patients—a mutation in a gene named **DYT1** (see “What research is being done?”). And it has been discovered that this gene is related not only to generalized dystonia, but also to some forms of focal dystonia. Note, however, that most dystonia, of any type, is not due to this gene and has an unknown cause.

Cervical dystonia, also called *spasmodic torticollis*, or *torticollis*, is the most common of the focal dystonias. In *torticollis*, the muscles in the neck that control the position of the head are affected, causing the head to twist and turn to one side. In addition, the head may be pulled forward or backward. *Torticollis* can occur at any age, although most individuals first experience symptoms in middle age. It often begins slowly and usually reaches a plateau. About 10 to 20 percent of those with *torticollis* experience a spontaneous remission, but unfortunately the remission may not be lasting.

Blepharospasm, the second most common focal dystonia, is the involuntary, forcible closure of the eyelids. The first symptoms may be uncontrollable blinking. Only one eye may be affected initially, but eventually both eyes are usually involved. The spasms may leave the eyelids completely closed causing functional blindness even though the eyes and vision are normal.

Cranial dystonia is a term used to describe dystonia that affects the muscles of the head, face, and neck. *Oromandibular dystonia* affects the muscles of the jaw, lips, and tongue. The jaw may be pulled either open or shut, and speech and swallowing can be difficult. *Spasmodic dysphonia* involves the muscles of the throat that control speech. Also called *spastic dysphonia* or *laryngeal dystonia*, it causes strained and difficult speaking or breathy and effortful speech. *Meige's syndrome* is the combination of blepharospasm and oromandibular dystonia

and sometimes spasmodic dysphonia. Spasmodic torticollis can be classified as a type of cranial dystonia.

Writer's cramp is a dystonia that affects the muscles of the hand, and sometimes the forearm, and only occurs during handwriting. Similar focal dystonias have also been called typist's cramp, pianist's cramp, and musician's cramp.

Dopa-responsive dystonia (DRD), of which *Segawa's dystonia* is an important variant, is a condition successfully treated with drugs. Typically, DRD begins in childhood or adolescence with progressive difficulty in walking and, in some cases, spasticity. In Segawa's dystonia, the symptoms fluctuate during the day from relative mobility in the morning to increasingly worse disability in the afternoon and evening as well as after exercise. The diagnosis of DRD may be missed since it mimics many of the symptoms of cerebral palsy.

What do scientists know about the dystonias?

Investigators believe that the dystonias result from an abnormality in an area of the brain called the basal ganglia where some of the messages that initiate muscle contractions are processed. Scientists suspect a defect in the body's ability to process a group of chemicals called neurotransmitters that help cells in the brain communicate with each other. Some of these neurotransmitters include:

- *GABA* (gamma-aminobutyric acid), an inhibitory substance that helps the brain maintain muscle control.

- *Dopamine*, an inhibitory chemical that influences the brain's control of movement.
- *Acetylcholine*, an excitatory chemical that helps regulate dopamine in the brain. In the body, acetylcholine released at nerve endings causes muscle contraction.
- *Norepinephrine* and *serotonin*, inhibitory chemicals that help the brain regulate acetylcholine.

Acquired dystonia, also called *secondary dystonia*, results from environmental or disease-related damage to the basal ganglia. Birth injury (particularly due to lack of oxygen), certain infections, reactions to certain drugs, heavy-metal or carbon monoxide poisoning, trauma, or stroke can cause dystonic symptoms. Dystonias can also be symptoms of other diseases, some of which may be hereditary.

About half the cases of dystonia have no connection to disease or injury and are called *primary* or *idiopathic dystonia*. Of the primary dystonias, many cases appear to be inherited in a dominant manner, that is, only one carrier parent need contribute the dystonia gene for the disease to occur, each child having a 50/50 chance of being a carrier. In dystonia, however, a carrier may or may not develop a dystonia and the symptoms may vary widely even among members of the same family. The product of one defective gene appears to be sufficient to cause the chemical imbalances that may lead to dystonia; but the possibility exists that another gene or genes and environmental factors may play a role.

Some cases of primary dystonia may have different types of hereditary patterns. Knowing the pattern of inheritance can help families understand the risk of passing dystonia along to future generations.

When do symptoms occur?

In some individuals, symptoms of a dystonia appear in childhood, approximately between the ages of 5 and 16, usually in the foot or in the hand. In generalized dystonia, the involuntary dystonic movements may progress quickly to involve all limbs and the torso, but the rate of progression usually slows noticeably after adolescence.

For other individuals, the symptoms emerge in late adolescence or early adulthood. In these cases, the dystonia often begins in upper body parts, with symptoms progressing slowly. A dystonia that begins in adulthood is more likely to remain as a focal or segmental dystonia.

Dystonias often progress through various stages. Initially, dystonic movements are intermittent and appear only during voluntary movements or stress. Later, individuals may show dystonic postures and movements while walking and ultimately even while they are relaxed. Dystonic motions may lead to permanent physical deformities by causing tendons to shorten.

In secondary dystonias due to injury or stroke, people often have abnormal movements of just one side of the body, which may begin at the time of the brain injury or sometime afterward. Symptoms generally plateau and

do not usually spread to other parts of the body.

Are there any treatments?

No one treatment has been found universally effective. Instead, physicians use a variety of therapies aimed at reducing or eliminating muscle spasms and pain.

- *Medication.* Several classes of drugs that may help correct imbalances in neurotransmitters have been found useful. But response to drugs varies among patients and even in the same person over time. The most effective therapy is often individualized, with physicians prescribing several types of drugs at different doses to treat symptoms and produce the fewest side effects. Note that not all of the medications mentioned below are currently available for patients in the United States.

Frequently, the first drug administered belongs to a group that reduces the level of the neurotransmitter acetylcholine. Drugs in this group include trihexyphenidyl, benzotropine, and procyclidine HCl. Sometimes these medications can be sedating, especially at higher doses, and this can limit their usefulness.

Drugs that regulate the neurotransmitter GABA may be used in combination with these drugs or alone in patients with mild symptoms. GABA-regulating drugs include the muscle relaxants diazepam, lorazepam, clonazepam, and baclofen.

Other drugs act on dopamine, a neurotransmitter that helps the brain fine-tune muscle movement. Some drugs which increase dopamine effects include levodopa/carbidopa and bromocriptine. DRD has been remarkably responsive to small doses of this dopamine-boosting treatment. On the other hand, patients have occasionally benefited from drugs that decrease dopamine, such as reserpine or the investigational drug tetrabenazine. Once again, side effects can restrict the use of these medications.

Anticonvulsants including carbamazepine, usually prescribed to control epilepsy, have occasionally helped individuals with dystonia.

- *Botulinum toxin.* Minute amounts of this familiar toxin can be injected into affected muscles to provide temporary relief of focal dystonias. First used to treat blepharospasm, such injections have gained wider acceptance among physicians for treating other focal dystonias. The toxin stops muscle spasms by blocking release of the excitatory neurotransmitter acetylcholine. The effect lasts for up to several months before the injections have to be repeated.
- *Surgery and other treatments.* Surgery may be recommended for some patients when medication is unsuccessful or the side effects are too severe. In selected cases, advanced generalized dystonias have been helped, at least temporarily, by surgical destruction of parts of the thalamus, a structure deep in the brain that helps control movement. Speech disturbance is

a special risk accompanying this procedure, since the thalamus lies near brain structures that help control speech. Surgically cutting or removing the nerves to the affected muscles has helped some focal dystonias, including blepharospasm, spasmodic dysphonia, and torticollis. The benefits of these operations, however, can be short-lived. They also carry the risk of disfigurement, can be unpredictable, and are irreversible.

Some patients with spasmodic dysphonia may benefit from treatment by a speech-language pathologist. Physical therapy, splinting, stress management, and biofeedback may also help individuals with certain forms of dystonia.

What research is being done?

The ultimate goals of research are to find the cause(s) of the dystonias so that they can be prevented and to find ways to cure or more effectively treat people now affected. The National Institute of Neurological Disorders and Stroke (NINDS), a unit of the Federal Government's National Institutes of Health (NIH), is the agency with primary responsibility for brain and neuromuscular research. NINDS sponsors research on dystonia both in its facilities at the NIH and through grants to medical centers throughout the country. Scientists at the National Institute on Deafness and Other Communication Disorders (NIDCD) are studying improved treatments for speech and voice disorders associated with dystonias. The National Eye Institute (NEI) supports work on the study of blepharospasm and related problems (see above), and the National Institute of Child Health and Human

Development (NICHD) supports work on dystonia including the rehabilitation aspects of the disorder.

Scientists at the NINDS laboratories have conducted detailed investigations of the pattern of muscle activity in persons with focal dystonias. One of the most important characteristics is the failure of reciprocal inhibition, a normal process in which muscles with opposite actions work without opposing each other. In dystonia, the tightening of muscles is associated with an abnormal pattern of muscles fighting each other. Other studies at the NINDS have probed the spinal reflex function and found abnormalities consistent with the defect in reciprocal inhibition. Other studies using EEG analysis and neuroimaging are probing brain activity and its relation to these observations.

The search for the gene or genes responsible for some forms of dominantly inherited dystonias continues. In 1989 a team of researchers mapped a gene for early-onset torsion dystonia to chromosome 9; the gene was subsequently named **DYT1**. In 1997 the team sequenced the **DYT1** gene and found that it codes for a previously unknown protein now called “torsin A.” The discovery of the **DYT1** gene and the torsin A protein provides the opportunity for prenatal testing, allows doctors to make a specific diagnosis in some cases of dystonia, and permits the investigation of molecular and cellular mechanisms that lead to disease.

The gene for Segawa’s dystonia has also been found. It codes for an enzyme important in the brain’s manufacture of dopamine.



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