

## REVIEW ARTICLE

## CURRENT CONCEPTS

## Dystonia

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THE TERM “DYSTONIA” WAS COINED BY OPPENHEIM IN 1911 TO DESCRIBE a disorder causing variable muscle tone and recurrent muscle spasm. This disorder was initially called *dystonia musculorum deformans*<sup>1,2</sup> and was later called primary torsion dystonia. Dystonia is a movement disorder that causes sustained muscle contractions, repetitive twisting movements, and abnormal postures of the trunk, neck, face, or arms and legs.<sup>3</sup> Many general physicians are unfamiliar with dystonia; they may often confuse it with spasticity or rigidity and sometimes may even mistakenly attribute it to psychogenic causes. Patients with dystonia often consult several physicians before the correct diagnosis is made. Some examples of misdiagnoses include those of cerebral palsy in a child with genetically determined dopa-responsive dystonia, dry eyes in a patient with blepharospasm, and cervical muscle strain in a patient with cervical dystonia. Given the recent advances concerning causes and treatment of dystonia, this disorder should be more widely and accurately recognized.

## CLINICAL FEATURES

Dystonia results from involuntary concomitant contraction of agonist and antagonist muscles, with overflow of unwanted muscle contractions into adjacent muscles. Dystonic movements can be either slow or rapid, can change during different activities or postures, and may become fixed in advanced cases. Tremor is sometimes present. Action dystonia refers to abnormal postures that occur during voluntary activity and are sometimes task-specific. Some localized dystonias respond to simple sensory tricks such as lightly touching the affected body part (*geste antagoniste*).

## CLASSIFICATION

Several classifications of dystonia are based on topographic distribution (Table 1), age at onset, cause, or genetics.<sup>3-7</sup> Classification according to the age at onset is important because when the disease begins in childhood or young adulthood, it usually progresses from focal limb dystonia to the severe generalized form, whereas dystonia that begins after about the age of 25 years usually involves craniocervical muscles, nearly always remains localized or segmental, and is usually not progressive.<sup>4</sup> The etiologic classification includes primary dystonia, secondary dystonia, dystonia-plus syndromes, and paroxysmal dystonia.<sup>5</sup> Genetic classification of dystonia is based on the loci of genes involved (Table 2). Dystonia loci DYT1 through DYT13 include autosomal dominant, autosomal recessive, and X-linked causes of primary dystonia and dystonia-plus syndromes. This rapidly evolving group of genetically determined dystonias has led to the increasing use of genetic counseling in families with these disorders.<sup>8</sup>

**PRIMARY DYSTONIA**

By definition, primary dystonias are unaccompanied by other neurologic abnormalities, except tremor and occasionally myoclonus, and have no known cause except for the genetic mutations that have been identified in some cases.<sup>4</sup> The prevalence of early-onset primary torsion dystonia is estimated in population studies to be as low as 0.7 per million or as high as 50 per million.<sup>9</sup> The prevalence among Ashkenazi Jews is 111 per million.<sup>10</sup> The prevalence of primary dystonia is higher when late-onset cases are included, with estimates ranging from 30 per million in a survey in China<sup>11</sup> to 7320 per million in a population-based study in Italy that focused on persons over the age of 50 years.<sup>12</sup> Cervical dystonia is the most common primary dystonia.<sup>9</sup> On the basis of one epidemiologic study,<sup>13</sup> an estimated 88,000 persons in the United States have primary focal dystonia, but this is presumed to be an underestimate because of the failure to recognize or diagnose dystonia. A video clip showing different forms of dystonia is available with the full text of this article at [www.nejm.org](http://www.nejm.org).

**PRIMARY GENERALIZED TORSION DYSTONIA**

Primary generalized torsion dystonia is a progressive, disabling disorder that usually begins in childhood and is linked to several genetic loci. Many cases are inherited as autosomal dominant traits caused by a guanine–adenine–guanine (GAG) deletion in the torsin A gene (DYT1 locus), resulting in the deletion of glutamate in torsin A,<sup>14</sup> a brain protein of unknown function whose highest concentrations are in the substantia nigra.<sup>6</sup> This genetic defect accounts for 80 percent of early limb-onset cases in Ashkenazi Jewish populations and 16 to 53 percent of cases in non-Jewish populations.<sup>4</sup> Penetrance is 30 to 40 percent, and clinical expression varies from generalized dystonia to occasional adult-onset focal dystonias.<sup>15-17</sup> It begins as a focal action dystonia before the middle of the third decade of life, with most cases beginning in childhood.<sup>18</sup> Because of its rarity and unfamiliar features, it is sometimes misdiagnosed as a psychogenic disorder. About 65 percent of cases progress to a generalized or multifocal distribution, 10 percent become segmental, and 25 percent remain focal.<sup>4</sup> Childhood-onset cases commonly evolve to generalized dystonia,<sup>19,20</sup> which produces severe disability owing to serious gait and posture abnormalities.

**Table 1. Topographic Classification of Dystonia.\***

Type of Dystonia	Region or Part Affected
Focal	Single region
Segmental	Two or more adjacent regions
Multifocal	Two or more nonadjacent regions
Generalized	Leg or legs, trunk, and one other region
Hemidystonia	Ipsilateral arm and leg

\* Adapted from Bressman.<sup>4</sup>**PRIMARY FOCAL DYSTONIA**

Primary focal dystonias are 10 times as common as primary generalized torsion dystonia<sup>19</sup> and are usually first seen by primary care physicians or subspecialists other than neurologists. Primary focal dystonia nearly always occurs in adults and may involve the neck, face, or arm, whereas the leg is rarely involved (Table 3). It typically begins in midlife or later and, with the exception of writer's cramp, is more common in women. The disorder typically progresses for one to two years and then follows a static course, although it occasionally spreads to adjacent muscle groups to become segmental. There is sometimes a family history of focal dystonia, but the genetic basis of these disorders is poorly understood. The loci of a small number of incompletely penetrant, autosomal dominant focal dystonias have been mapped, including DYT6, DYT7, and DYT13 (Table 2). Mutations in the torsin A gene (at the DYT1 locus) have also been identified in occasional patients with adult-onset focal dystonia.<sup>15-17</sup>

Cervical dystonia (Fig. 1A), also known as spasmodic torticollis, is the most common focal dystonia. It usually begins between the ages of 30 and 50 years, often with initial neck stiffness and restricted head mobility. It is therefore often misdiagnosed as a musculoskeletal disorder. Abnormal head postures follow, sometimes associated with irregular head tremor. Neck and shoulder pain occur in 75 percent of cases. Sensory tricks such as lightly touching the face or chin reduce the severity of symptoms in most patients. The differential diagnosis includes essential head tremor, tardive dystonia in which retrocollis is common, anterocollis caused by cervical myopathy or multiple system atrophy, and secondary torticollis associated with neck injury, atlantoaxial dislocation, cervical disk disease, spinal-cord neoplasm, or soft-tissue infections of the neck.

**Table 2. Genetic Classification of Dystonias.\***

Designation	Other Names	Locus	Chromosome	OMIM No.†	Gene and Function	Mutation	Inheritance	Penetrance	Age at Onset	Clinical Features
Dystonia 1	Primary torsion dystonia; idiopathic torsion dystonia; Oppenheim dystonia; dystonia musculorum deformans I; TOR1A	DYT1	9q34	128100	Torsin A; unknown	GAG deletion	Autosomal dominant	30–40%	Childhood or early adulthood (before 26 yr)	Often starts as focal limb dystonia (commonly action dystonia of one foot); often generalized
Dystonia 2	Autosomal recessive primary torsion dystonia	DYT2	Unknown	224500	Unknown	Unknown	Autosomal recessive	Unknown	Childhood	Segmental or generalized dystonia
Dystonia 3	X-linked dystonia–parkinsonism; lubag	DYT3	Xq13.1	314250	TAF1, encoding a transcription factor; may regulate expression of dopamine D2 receptors	Unknown	X-linked	100% by 5th decade	12–52 Yr (mean, 37.9)	Male patients have focal dystonia followed by segmental or generalized dystonia; parkinsonism develops later in 50% of cases; endemic in Panay, Philippines
Dystonia 4	Torsion dystonia 4; non-DYT1 primary torsion dystonia	DYT4	Unknown	128101	Unknown	Unknown	Autosomal dominant	Unknown (affects 40% of patients' offspring who are older than 40 yr)	13–37 Yr	Primarily laryngeal ("whispering") dystonia; sometimes cervical; often generalized; psychiatric symptoms present in some cases; reported in one large Australian family
GCH1 (formerly Dystonia 5)	Dopa-responsive dystonia; Segawa syndrome; hereditary progressive dystonia with marked diurnal variation	GCH1 (formerly DYT5)	14q22.1–14q22.2 (11p15.5 for tyrosine hydroxylase)	128230	Guanosine triphosphate cyclohydrolase; bipterin in synthesis (cofactor for dopamine synthesis); also rarely tyrosine hydroxylase	Variable (>60 mutations reported)	Autosomal dominant; autosomal recessive for tyrosine hydroxylase	30% (possibly higher in females)	Usually childhood	Dystonia; parkinsonism; may mimic cerebral palsy; diurnal variation; dramatic response to levodopa

Dystonia 6	Adolescent-onset primary torsion dystonia of mixed type	DYT6	8p21-8p22	602629	Unknown	Unknown	Autosomal dominant	30%	Average age, 19 yr	Focal (cervical, cranial, or limb) or segmental; may become generalized; reported in Amish families
Dystonia 7	Adult-onset focal primary torsion dystonia	DYT7	8p11.3	602124	Unknown	Unknown	Autosomal dominant	Incomplete (<40%)	Adulthood (28-70 yr)	Focal dystonia (cervical dystonia, writer's cramp, laryngeal dystonia); hand tremors; not generalized; reported in German families
Dystonia 8	Paroxysmal dystonic choreoathetosis; paroxysmal nonkinesogenic dyskinesia; Mount-Reback syndrome	DYT8	2q33-2q36	118800	Unknown	Unknown	Autosomal dominant	Incomplete	Childhood to early adulthood	Episodes of dystonia and chorea or dyskinesias lasting 2 min to 4 hr triggered by stress, alcohol, caffeine, nicotine
Dystonia 9	Paroxysmal choreoathetosis with episodic ataxia and spasticity; choreoathetosis, spasticity, and episodic ataxia	DYT9 (also known as CSE)	1p13.3-1p21	601042	Unknown	Unknown	Autosomal dominant	Unknown	Childhood (2-15 yr)	Chronic spastic paraplegia plus episodes of dystonia, choreoathetosis, paresthesias, and diplopia triggered by exercise, stress, alcohol
Dystonia 10	Paroxysmal kinesogenic choreoathetosis; paroxysmal kinesogenic dyskinesias; periodic dystonia	DYT10	16p11.2-16q12.1	128200	Unknown	Unknown	Autosomal dominant	Incomplete	Childhood (6-16 yr)	Episodes of dystonia and choreoathetosis triggered by sudden movements

**Table 2.** (Continued.)

Designation	Other Names	Locus	Chromosome	OMIM No.†	Gene and Function	Mutation	Inheritance	Penetrance	Age at Onset	Clinical Features
Dystonia 11	Myoclonus–dystonia; alcohol-responsive dystonia	DYT11	7q21–7q31	159900	ε-Sarcoglycan	Variable (heterozygous loss of function)	Autosomal dominant	Incomplete; higher when inherited paternally (imprinting)	Variable; can be early childhood	Myoclonus plus dystonia; improves with alcohol ingestion
Dystonia 12	Rapid-onset dystonia–parkinsonism	DYT12	19q13	128235	Na <sup>+</sup> /K <sup>+</sup> -ATPase α3 subunit (ATP1A3)	Unknown	Autosomal dominant	Incomplete	Variable (childhood to adulthood)	Acute or subacute onset of generalized dystonia plus parkinsonism
Dystonia 13	Focal dystonia with cranio-cervical features	DYT13	1p36.13–1p36.32	607671	Unknown	Unknown	Autosomal dominant	58%	Variable (5 yr to adulthood; average, 15 yr)	Focal or segmental dystonia (cranial, cervical, or upper limb); mild in severity; rarely generalized; reported in an Italian family
DFN-1/MTS	Deafness–dystonia syndrome 1; Mohr–Tranebjærg syndrome; XL dystonia optic atrophy	DDP	Xq22	304700	Dystonia–deafness peptide; mitochondrial protein import	Variable	X-linked	Incomplete in female carriers (incompletely skewed X-inactivation)	Childhood	Dystonia, sensorineural hearing loss, spasticity, mental retardation, cortical blindness; female carriers may present with adult-onset focal dystonia without deafness
LHON–dystonia	Leber's hereditary optic neuropathy plus dystonia	Mitochondrial DNA	Mitochondrial DNA	516006	NADH-ubiquinone oxidoreductase, subunit ND6 (NADH dehydrogenase, subunit 6); mitochondrial complex I	Point mutation	Maternal	Incomplete	Variable	Dystonia, optic atrophy, or both

\* Adapted in part from de Carvalho Aguiar and Ozelius<sup>6</sup> and Nemeth.<sup>7</sup>

† For additional references, see Online Mendelian Inheritance in Man (OMIM), at [www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM).

**Table 3. Primary Adult-Onset Focal Dystonias.**

Type of Dystonia	Main Clinical Features	Common Misdiagnoses
Cervical dystonia (spasmodic torticollis)	Abnormal head posture Head tremor Neck pain	Muscle strain Cervical disk disease Osteoarthritis
Blepharospasm	Increased blink rate Forced eye closure Difficulty opening eyes	Myasthenia gravis Dry eyes
Oromandibular dystonia	Jaw clenching (bruxism) Jaw in open position Lateral jaw shift	Temporomandibular joint syndrome Myasthenia gravis Dental malocclusion Edentulous movements
Orofacial dystonia	Action dystonias involving lips, tongue, or pharynx	Tic disorders
Spasmodic dysphonia		Chronic laryngitis, vocal-cord polyps, voice tremor, psychogenic causes
Adductor type	Voice breaks and strain	
Abductor type	Breathy voice	
Mixed type	Features of both	
Limb dystonia	Action dystonias affecting writing, playing musical instruments, handling tools, walking	Nerve entrapment Overuse syndromes Muscle cramps
Axial dystonia	Movements of shoulders, back, or abdomen	Myoclonus Motor tics Psychogenic causes

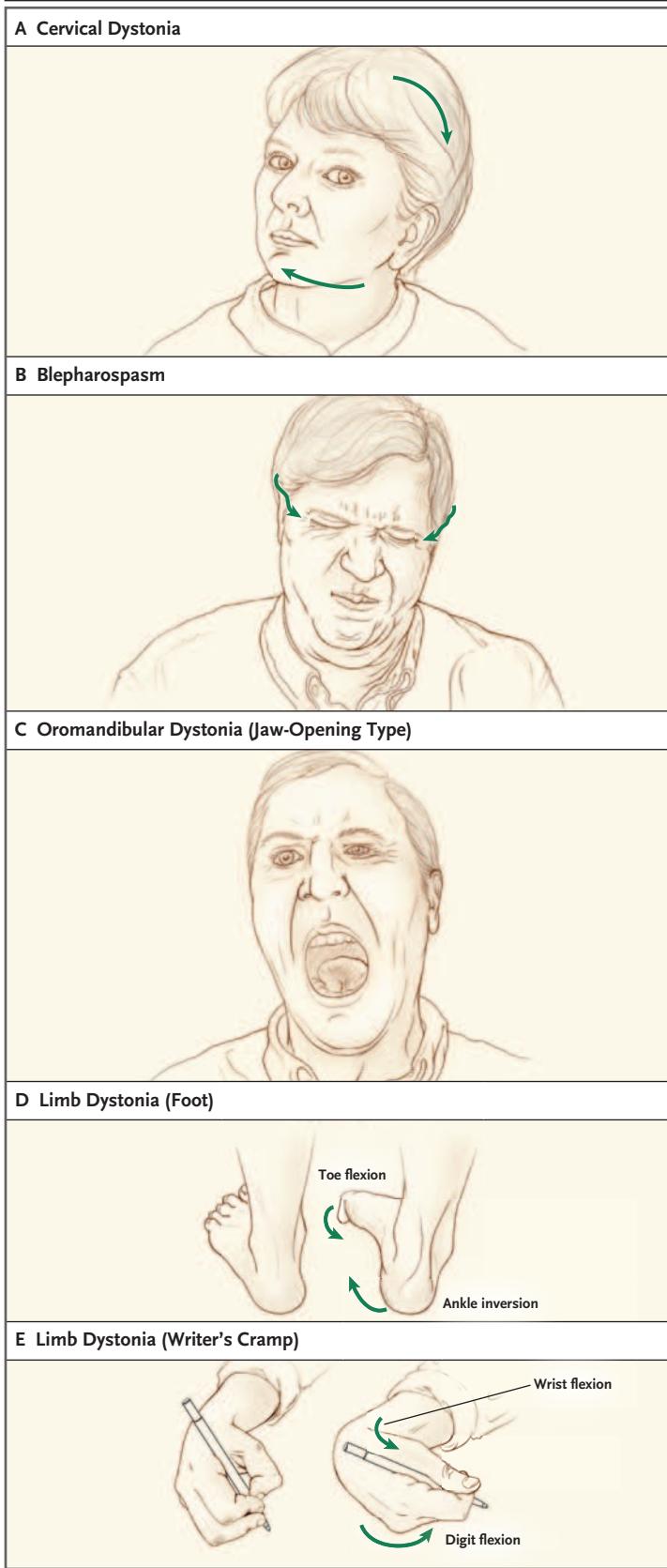
Cranial dystonia may involve the eyelids, jaw, vocal cords, face, tongue, platysma, or pharynx. It usually begins after the age of 40 years. Blepharospasm (Fig. 1B) is the most common cranial dystonia, causing an increased blink frequency, forced eye closure, or difficulty opening the eyes. Symptoms are typically aggravated by bright light, reading, or driving, and they can be severe enough to cause functional blindness. Blepharospasm is often confused with tic disorders or eyelid ptosis owing to myasthenia gravis. Secondary blepharospasm occurs in patients with tardive dyskinesia, Parkinson's disease, and in rare instances, structural brainstem lesions. Dry eyes caused by eyelid or lacrimal disorders is a very infrequent cause of chronic blepharospasm.

Oromandibular dystonia causes involuntary clenching, opening, or deviation of the jaw (Fig. 1C). Muscles of the mouth, tongue, or neck are frequently also involved. Severe cases may cause jaw pain, dysarthria, difficulty chewing, dysphagia, and dental trauma. The differential diagnosis includes temporomandibular joint disorders, bruxism, edentulous mouth movements, and tardive dyskinesia.

Spasmodic dysphonia is an action dystonia in which speaking precipitates adduction or abduc-

tion of the vocal cords. Adductor dysphonia accounts for 90 percent of the cases and is due to overcontraction of the thyroarytenoid muscles, which causes strained speech and voice breaks. In abductor dysphonia, posterior cricoarytenoid overcontraction separates the vocal cords, causing an intermittent, breathy voice. Spasmodic dysphonia is commonly misdiagnosed as a psychogenic disorder. The differential diagnosis includes essential voice tremor, facial dystonias that affect the voice, and structural or inflammatory vocal-cord disorders.

Limb dystonia is a less frequent focal dystonia, which in adults, involves the arm more frequently than the leg (Fig. 1D and 1E). It causes involuntary twisting, flexion, or extension postures of the arms or legs or digits. In the arms these typically occur during skilled manual activities and are also known as occupational cramp disorders. In writer's cramp, involuntary hand postures impair handwriting. Similar problems occur in pianists and string musicians.<sup>21</sup> Unlike orthopedic overuse syndromes with which they are often confused, limb dystonia responds poorly to rest. Limb dystonia of the foot can be a presenting sign of Parkinson's disease. In rare cases, focal limb dystonia is associated with structur-



**Figure 1. Abnormal Postures in Dystonia.**

Panel A shows cervical dystonia causing combined head rotation and backward head deviation. Panel B shows blepharospasm causing involuntary eye closure with reactive lower facial grimacing. Panel C shows oromandibular dystonia causing involuntary jaw opening. Panel D shows lower-limb dystonia causing involuntary ankle inversion and toe flexion, and Panel E shows upper-limb dystonia causing flexion dystonia of the wrist and digits while the patient is writing.

al lesions of the basal ganglia, corticobasal degeneration, or progressive supranuclear palsy, although it usually occurs in association with other major neurologic findings.

**SECONDARY DYSTONIA**

Secondary dystonia is a large and diverse group of disorders with many causes, including hereditary degenerative diseases with known neuropathological features, drug-induced dystonia, and dystonia caused by acquired structural abnormalities.

**HEREDODEGENERATIVE DISORDERS**

Other neurologic abnormalities are usually prominent in hereditary degenerative disorders, which are a heterogeneous group of degenerative and metabolic disorders, many of which are genetic.<sup>22</sup> Distinctive pathological abnormalities usually involve the basal ganglia, thereby also producing parkinsonism and other extrapyramidal signs. A partial list is provided in Table 4, and more complete lists and references are available elsewhere.<sup>5-7,22</sup>

**DRUG-INDUCED DYSTONIA**

Acute drug-induced dystonia is caused by levodopa, dopamine agonists, antipsychotic drugs, anti-convulsant agents, serotonin-reuptake inhibitors, and rarely by other miscellaneous drugs. Persistent tardive dystonia may occur after prolonged use of dopamine-receptor–blocking antipsychotic drugs and metoclopramide. Dystonia may also occur as a result of the toxic effects of manganese, carbon monoxide, carbon disulfide, and other chemicals.

**ACQUIRED STRUCTURAL LESIONS**

Acquired brain lesions may produce either hemidystonia or focal limb dystonia, and the findings on brain imaging are frequently abnormal. Lesions of the basal ganglia involving the putamen and thalamus are particularly common<sup>23</sup> and occur after perinatal injury, kernicterus, infarcts, hem-

**Table 4. Heredodegenerative and Metabolic Disorders Sometimes Causing Dystonia.\***

Wilson's disease
Parkinsonian syndromes
Parkinson's disease
Juvenile parkinsonism (PARKIN mutations)
Multisystem atrophy
Corticobasal degeneration
Progressive supranuclear palsy
Globus pallidus degenerations
Pantothenate kinase deficiency due to PANK2 mutations†
Familial basal ganglia calcifications
Huntington's disease
Spinocerebellar degenerations
Lysosomal storage disorders
Dystonic lipidosis
Ceroid lipofuscinosis
Metachromatic leukodystrophy
GM1 and GM2 gangliosidosis
Neimann–Pick disease type C
Krabbe's disease
Pelizaeus–Merzbacher disease
Organic aminoacidurias
Glutaric acidemia
Homocysteinuria
Hartnup's disease
Methylmalonic aciduria
Mitochondrial disorders
Leigh's disease
Leber's plus dystonia
X-linked dystonia–deafness
Neuroacanthocytosis
Lesch–Nyhan syndrome
Ataxia–telangiectasia

\* Adapted from Fahn et al.<sup>5</sup> and Friedman and Standaert.<sup>22</sup>

† This abnormality was formerly known as Hallervorden–Spatz disease.

orrhage, infection, trauma, anoxia, multiple sclerosis, and brain tumors.<sup>24</sup>

Peripheral trauma is sometimes followed by typical focal dystonia. However, in some cases trauma is followed by abnormal, fixed postures that differ from dystonia in that they begin immediately after the trauma, do not involve involuntary movements, are characterized by pain with features of the complex regional pain syndrome, do not respond to sensory tricks, and have a lim-

ited response to treatment with botulinum toxin.<sup>25,26</sup> The relation between these postures and true dystonia is uncertain and controversial.<sup>27,28</sup> Although primary dystonia is often mistakenly attributed to psychological causes, psychogenic dystonia has been documented, often occurring abruptly after peripheral trauma.<sup>29</sup>

#### DYSTONIA-PLUS SYNDROMES

Several rare genetic dystonia-plus syndromes are distinguished from the heredodegenerative disorders because they are not associated with known neuropathological findings.<sup>5</sup> These disorders are associated with other neurologic signs such as parkinsonism in dopa-responsive dystonia or rapid-onset dystonia–parkinsonism and myoclonus in myoclonus–dystonia.<sup>4,6,7,30,31</sup>

Dopa-responsive dystonia (locus DYT5) is a rare disorder presenting in early childhood with foot dystonia, gait abnormality, and hyperreflexia, followed by progressive generalized dystonia.<sup>32</sup> Diurnal fluctuation with worsening of symptoms late in the day is a unique feature. Early development of patients is normal, a characteristic that distinguishes this type of dystonia from spastic cerebral palsy with which it is often confused. In rare cases, symptoms may be limited to focal dystonia, and parkinsonism occasionally occurs in adult-onset forms. The hallmark of this disorder is a dramatic and sustained response to levodopa. It is autosomal dominant, caused by a point mutation in the gene for guanosine triphosphate cyclohydrolase 1, which is necessary for the synthesis of tetrahydrobiopterin, a cofactor in dopamine synthesis. In rare instances, autosomal recessive mutations in the tyrosine hydroxylase gene, also required for dopamine synthesis, cause a similar phenotype. There are no neuropathological changes in dopamine-containing neurons of the substantia nigra, and the results of <sup>18</sup>F-fluorodopa positron-emission tomography are normal. The differential diagnosis includes juvenile parkinsonism, in which dystonia may be prominent early in the disease, primary generalized torsion dystonia, which shows no response to levodopa, and developmental motor disorders with dystonia.

Myoclonus–dystonia (DYT11 locus) is a rare autosomal dominant disorder caused by a mutation in the gene encoding  $\epsilon$ -sarcoglycan.<sup>33</sup> It begins in childhood or adolescence and results in dystonia of the arms, trunk, and bulbar muscles with brief myoclonic muscle jerks that are de-

creased by the ingestion of alcohol.<sup>34</sup> Rapid-onset dystonia–parkinsonism (DYT12 locus) is a rare autosomal dominant disorder that begins in adolescence or young adulthood with the rapid appearance of dystonia and parkinsonism, followed by a plateau in symptoms. There is no nigrostriatal neuronal loss or clinical response to levodopa.<sup>35</sup>

#### PAROXYSMAL DYSTONIA

Paroxysmal dystonias (loci DYT8 through DYT10) are rare disorders that begin in childhood or young adulthood and are characterized by episodic dystonia and other involuntary movements without symptoms or neurologic findings between episodes. Their relation to other dystonias is uncertain since they overlap clinically with other episodic disorders such as epilepsy and episodic ataxia and may be ion-channel disorders. They are broadly divided into brief kinesigenic dystonias precipitated by sudden movement that usually respond to anticonvulsant agents, more prolonged spontaneous dystonias that are more resistant to treatment, exercise-induced dystonia, and mixed forms.<sup>36</sup> A gene locus has been found in several families (Table 2), but other genetic types with unknown loci exist and cases secondary to acquired brain lesions such as multiple sclerosis also occur. Paroxysmal dystonia must be distinguished from seizures, nonepileptic pseudoseizures, and psychogenic symptoms.

#### PATHOPHYSIOLOGY

The pathophysiology of primary dystonia is unknown. Lesions of the putamen and thalamus may cause secondary dystonia,<sup>23</sup> but pathological abnormalities have not been identified in primary dystonia, suggesting that unidentified biochemical or neurophysiologic abnormalities may be responsible. A role for dopamine is suggested by the therapeutic effect of levodopa in dopa-responsive dystonia, dystonia caused by levodopa in Parkinson's disease, dystonia produced by dopamine-receptor–blocking antipsychotic drugs, and the frequent association of dystonia with parkinsonism. Dystonia is characterized by impaired inhibition at multiple levels of the central nervous system.<sup>37</sup> Disturbed “surround” inhibition, with failure to suppress neuronal excitability in regions surrounding activated neural circuits, may cause overflow movements in adjacent muscles.<sup>38</sup> The sensorimotor representation of

affected body parts is enlarged in the cerebral cortex of patients with focal dystonia.<sup>39,40</sup> However, although motor and sensory functions of basal ganglia appear altered,<sup>41</sup> it is not known whether these changes are primary or secondary. Positron-emission tomography<sup>41</sup> and globus pallidus recordings<sup>42</sup> show abnormal patterns of neuronal activity in the basal ganglia, the importance of which is supported by circuit abnormalities in the basal ganglia recently identified pathologically in X-linked recessive dystonia–parkinsonism, or lubag (DYT3 locus).<sup>43</sup>

#### EVALUATION

The evaluation begins with history taking and an examination to rule out secondary dystonia.<sup>22</sup> Birth, developmental, medication, toxin, trauma, and family histories are important. When other neurologic findings are present, magnetic resonance imaging (MRI) of the brain and laboratory testing for an underlying structural, degenerative, or metabolic disorder are indicated. Wilson's disease should be ruled out by measuring serum ceruloplasmin levels and 24-hour urinary copper levels and by slit-lamp examination. Dopa-responsive dystonia may be ruled out with a three-week trial of levodopa. In adults in whom dystonia is the only neurologic abnormality, a search for rare degenerative or metabolic disorders is unlikely to be fruitful. The finding of a family history of focal or generalized dystonia suggests the presence of genetically determined dystonia. Genetic testing for mutations at the DYT1 locus is commercially available. It should be considered in patients with generalized or focal dystonia that begins before the age of 26 years. It should also be considered in patients with limb dystonia beginning after the age of 26 years who have a relative in whom dystonia began before the age of 26 years.<sup>18</sup> The presence of hemidystonia suggests a structural brain lesion, which warrants MRI of the brain, whereas imaging of the cervical spine is indicated for atypical forms of cervical dystonia.

#### TREATMENT

##### PHARMACOTHERAPY

Except for dopa-responsive dystonia and Wilson's disease, there is no specific pharmacologic treatment for dystonia. Patients with generalized or

focal dystonia of unknown cause should undergo a trial of carbidopa–levodopa (one 25/100 mg tablet three times a day) to establish or rule out dopa-responsive dystonia. High-dose anticholinergic treatment with trihexyphenidyl (6 to 80 mg per day) or bntropine (4 to 8 mg per day) was partially effective in up to 40 to 50 percent of patients with primary or secondary dystonia.<sup>44,45</sup> Children can tolerate higher doses than adults can, with greater benefit and fewer side effects.<sup>44,45</sup> Benzodiazepines, baclofen, diphenhydramine, carbamazepine, mexiletine, gabapentin, dopamine agonists, and dopamine antagonists have been used in open-label trials without consistent benefit. Tetrabenazine (Xenazine, Cambridge Laboratories), a presynaptic depletor of dopamine and a weak dopamine-receptor–blocking agent that has not been approved by the Food and Drug Administration for use in the United States, produced marked improvement in two thirds of patients with focal and generalized dystonia in a large, uncontrolled retrospective study,<sup>46</sup> but it was associated with frequent side effects. Intrathecal baclofen has been used with mixed success in children and adults whose dystonia is combined with spasticity.<sup>47,48</sup>

#### BOTULINUM TOXIN

Botulinum toxin serotypes A and B inhibit the release of acetylcholine into the neuromuscular junction. When injected into dystonic muscles, they reduce muscle spasm without systemic side effects. This is the treatment of choice for cervical dystonia, blepharospasm, spasmodic dysphonia, oromandibular dystonia, and limb dystonia,<sup>49</sup> because it provides long-term benefit in 70 to 90 percent of patients. Similar benefit has been seen with either serotype A or B in patients with cervical dystonia.<sup>50</sup> It may also be used in patients with generalized or multifocal dystonia to treat selected muscles. The frequency of neutralizing antibody-mediated resistance to botulinum toxin serotype A has declined since the introduction of a commercial preparation containing a smaller amount of complex protein.<sup>51</sup>

#### SURGERY

Focal dystonias such as cervical dystonia and blepharospasm have been treated by selective peripheral denervation of muscle, with inconsistent benefit. Stereotactic thalamotomy and pallidotomy were previously used to treat primary dystonia.

Currently, deep-brain stimulation of the globus pallidus is being introduced for the treatment of medically refractory dystonia. After encouraging results in open-label trials,<sup>52</sup> this procedure was performed in 22 patients with primary torsion dystonia, with double-blind evaluation up to 12 months after surgery.<sup>53</sup> Dystonia rating scales and disability scores improved by approximately 50 percent at 12 months. The mechanism of action of deep-brain stimulation is uncertain but may result from the suppression of irregular patterns of neuronal activity.<sup>42</sup> Although the experience with this therapy for cervical dystonia is much more limited, promising results have been reported.<sup>54</sup> Deep-brain stimulation is much less effective in patients with hemidystonia because of the presence of focal brain lesions, but it has been effective in patients with tardive dystonia.<sup>55</sup>

#### PHYSICAL THERAPIES

Muscle stretching and strengthening may be used to avoid contractures, and mechanical assistive devices may reduce disability. Sensory training<sup>56,57</sup> and limb-immobilization techniques<sup>58</sup> have been offered for the treatment of limb dystonia but are currently of unproven benefit.

Information on dystonia may be found online at [www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM). Additional information can be found online at [www.dystonia-foundation.org](http://www.dystonia-foundation.org) and at [www.wemove.org](http://www.wemove.org).

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A video clip showing different forms of dystonia is available with the full text of this article at [www.nejm.org](http://www.nejm.org).

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