The Focal Dystonias: Current Views and Challenges for Future Research

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Abstract

The most common forms of dystonia are those that develop in adults and affect a relatively isolated region of the body. Although these adult-onset focal dystonias are most prevalent, knowledge of their etiologies and pathogenesis has lagged behind some of the rarer generalized dystonias, where the identification of genetic defects has facilitated both basic and clinical research. This summary provides a brief review of the clinical manifestations of the adult-onset focal dystonias, focusing attention on less well-understood clinical manifestations that need further study. It also provides a simple conceptual model for the similarities and differences among the different adult-onset focal dystonias, as a rationale for lumping them together as a class of disorders while at the same time splitting them into subtypes. The concluding section outlines some of the most important research questions for the future. Answers to these questions are critical for advancing our understanding of this group of disorders, and for developing novel therapeutics.

INTRODUCTION

The dystonias are a group of disorders with many different clinical manifestations, but certain features in common.1–3 The shared features are involuntary sustained or intermittent muscle contractions causing abnormal postures and/or repetitive movements. Dystonic movements often are patterned or twisting, but a tremor-like movement occasionally predominates. The most common forms are the adult-onset focal dystonias (AOFD), involving the neck (cervical dystonia, CD), upper face (blepharospasm, BL) mouth and jaw (oromandibular, OMD), larynx (LD), or a limb (e.g. writer’s cramp and other focal hand dystonias).

Many prior reviews have addressed typical clinical aspects and treatment of AOFD.4–15 In this summary we focus instead on some of the less well-characterized features and important unanswered questions for research. The first part addresses issues relevant to specific
ADULT-ONSET FOCAL DYSTONIAS

Cervical Dystonia (CD)

Clinical features—CD is characterized by excessive involuntary activity of neck muscles leading to abnormal movements of the head and neck pain. Several overlapping manifestations have been described. The head may turn to the right or left (torticollis), it may tilt to one side (laterocollis), or it may tilt upwards (retrocollis) or downwards (anterocollis). In addition to abnormal head positions, there may be tremulous movements or spasmodic jerking of the head.

Etiology & Pathogenesis—There is increasing evidence that CD is etiologically heterogeneous. Early clues for this heterogeneity came from recognition that certain manifestations are associated with specific diseases. For example, predominant anterocollis or retrocollis seem more common in Parkinson’s disease or other parkinsonian syndromes than in idiopathic CD, although formal studies comparing different populations are lacking. Similarly, fixed manifestations are uncommon for idiopathic CD and more often are due to syringo or psychogenic causes.

Genetic etiologies have received considerable attention because of the existence of rare families with multiple affected members. Additionally, CD may occur among patients carrying defects in genes more commonly associated with generalized dystonia such as the TOR1A gene at the DYT1 locus or the THAP1 gene at the DYT6 locus. Three new candidate genes for CD recently have been identified by exome sequencing: CIZ1, GNAL, and ANO3. The last gene appears to be associated with tremulous CD, illustrating the importance of clinical subtypes. Although these genes account for relatively few cases, a genetic basis may explain many sporadic cases, as 10–20% of patients have at least one family member with AOFD.

There are also important non-genetic causes. For example, exposure to dopamine receptor antagonists causes both acute dystonic reactions and tardive syndromes with prominent dystonia. There also are associations with trauma or autoimmune disease, although causal links have not been established. Finally, CD may result from focal lesions. These apparently acquired forms of CD may result from non-genetic mechanisms, or they may reflect combination of an acquired insult and genetic predisposition.

The exact areas of the nervous system responsible for causing CD remain uncertain. CD may be secondary to local brain injury, and lesions have been identified in many regions. In idiopathic CD where focal lesions are absent, voxel-based morphometry (VBM) also has revealed abnormalities in many regions. Functional imaging of regional blood flow with positron-emission tomography (PET) or metabolic mapping with fluorodeoxyglucose PET have pointed to different regions as well.

Among the regions identified by imaging, most studies have revealed no obvious histopathological abnormalities. However, the numbers of brains studied has been small, and the methods applied not suitable for detecting subtle abnormalities. Two recent studies revealed subtle abnormalities in the cerebellum. One revealed low Purkinje neuron densities in CD, and another revealed Purkinje neuron loss and torpedo bodies to be more prominent in CD with tremor compared to tremor alone.
Therapeutic challenges—Injections of botulinum toxin provide relief from abnormal movements and pain. Resistance may develop with long term use, but appears uncommon with modern preparations of the toxin. The main drawbacks include the requirement for injections every 3–4 months, and occasional transient side effects such as dysphagia or head drop. There also is increasing recognition of the need for higher doses over time and low levels of satisfaction among some patients.

Although it usually is possible to achieve good therapeutic outcomes with botulinum toxin, a few subtypes seem more challenging. Patients with predominant anterocollis are more difficult to treat, possibly due to contraction of the deep pre-vertebral paraspinal muscles that cannot be reached without radiographic guidance. Even with guidance, many patients with anterocollis still fail to respond, so the reasons for poor outcomes in this subgroup remain unclear.

The use of botulinum toxins has substantially reduced the numbers of patients undergoing surgical procedures such as peripheral denervation, although surgery is still useful in some cases. Deep brain stimulation (DBS) has gained increasingly popularity because of proven and long-term efficacy in generalized primary dystonias, and some secondary dystonias. It is gaining increasing popularity for AOFD, although patient selection criteria are not well established.

The potential benefits of physical therapy are not well characterized. Many patients request it, and many providers recommend it, because it seems intuitively useful. However, optimal methods have not been systematically studied, with different therapists each promoting different strategies and techniques based on personal experience. There are no large-scale blinded studies comparing strategies or demonstrating efficacy. In fact, some of the most objective studies have failed to demonstrate benefit. Whether this reflects the futility of physical therapy, the use of inappropriate methods, or insensitive outcome measures remains unknown.

Blepharospasm (BL)

Clinical features—BL is characterized by involuntary spasms of the orbicularis oculi muscles. There are several overlapping phenotypes. The most characteristic is prolonged spasms of eye closure. Another manifestation is frequent blinking, which may be isolated or associated with spasms. Increased blinking often precedes the development of tonic spasms, but isolated increased blinking also may be a distinct disorder. Discriminating normal blinks from blinks of blepharospasm is challenging because criteria discriminating a blink versus a short spasm have not been established.

Another phenotype is failure to voluntarily open the eyes with no apparent spasm of the orbicularis oculi. This phenomenon is sometimes called “apraxia” of eyelid opening. It may occur in patients who have had more obvious orbicularis oculi spasms, it may occur with other disorders, or it may occur in isolation. In some cases, it may be a manifestation of dystonia due to contraction of the pretarsal portion of the orbicularis oculi, antagonizing eyelid opening. However, “apraxia” is more properly due to failure of levator contraction, and therefore it is not considered dystonic.

Etiology & Pathogenesis—The etiology and pathogenesis of BL is multifactorial. Epidemiological studies suggest a genetic component. BL may occur in the setting of generalized or segmental dystonia associated with some of genes described above for CD, but no genes for isolated BL have been found. Since there is considerable phenotypic overlap between familial and sporadic BL, many cases of sporadic BL may have a genetic influence.
Any model for pathogenesis should take into account several non-genetic factors. BL is associated with focal lesions in the nervous system, exposure to certain drugs, and degenerative disorders. Eye disorders, particularly dry eye, commonly precede BL. Coffee appears to have a protective effect, although a mechanistic explanation has not been established.

Another common feature of BL is photophobia, which might also be called photoulodynia since it refers to pain induced by light. Some wavelengths of light are worse than others. The intrinsically photosensitive retinal ganglion cells which contain melanopsin, a light-sensitive pigment, might be the mediator. Melanopsin has a peak absorption in the blue area, and may explain observations that blue light is most uncomfortable. Photophobia has been reported in blind patients, so it may not depend on the pathway that leads to conscious vision. A portion of the melanopsin cells project directly to the thalamic nuclei (posterior, lateral posterior, intergeniculate) that are responsive to pain. A potentially relevant finding is one 18-fluorodeoxyglucose PET study showing that BL patients with photophobia compared to patients without photophobia had hypermetabolism of the ventral anterior and ventral lateral thalamus. Whether the melanopsin pathway is affected in BL remains to be established.

The functional anatomy of BL also remains unclear. BL rarely can result from focal lesions, and presumably causative lesions have been identified in several areas. Several regions also have been identified by VBM, PET, and functional MRI (fMRI). Physiological studies have shown hyperexcitability of the blink reflex in BL. More recently, an increase blink reflex plasticity has been found. Pairing high frequency stimulation of the supraorbital nerve with the R2 component of the blink reflex leads to an effect that resembles long term potentiation, and this has been reported to be exaggerated in one study and normal in another. Additionally, the temporal discrimination threshold is elevated in BL patients. All of these features are found also in other AOFD.

**Therapeutic challenges**—Spasms and blinking generally respond to injections of botulinum toxin. The main limitations include the need for injections approximately every 3 months and transient side effects such as ptosis, diplopia, or dry eyes. The phenotype of “apraxia” of eyelid opening is more difficult to treat. Some patients respond to injections of botulinum toxin into the pre-tarsal orbicularis oculi, and some respond to myectomy. Other surgical approaches use methods developed for ptosis repair, including levator shortening and removal of redundant lid tissue. An intriguing possibility involves local injection of bupivacaine into the levator, causing muscle damage, followed by regeneration that might produce muscle shortening and stiffening (A. Scott, personal communication). This strategy did not work for ptosis in patients with chronic progressive external ophthalmoplegia, but may have been due to insufficient doses.

DBS is another surgical method sometimes used in the treatment of BL. This approach is offered when medical therapy fails or when BL is accompanied by dystonia elsewhere. BL responds in some, but not others. Curiously, orbicularis oculi spasms and apparent apraxia can be induced by DBS in some patients, where they did not previously exist. The reasons for this phenomenon are unclear. For all surgical procedures there are many unresolved questions including patient selection criteria, and safety and durability of benefits.

Another area of therapeutics that has not received much attention involves eyeglasses. Although many patients report benefit from wearing dark glasses, there are few relevant
studies. If the melanopsin pathways play an important role, FL-41 tinted glasses (rose colored) that block blue light might be most effective.\textsuperscript{125}

### Laryngeal dystonia (LD)

**Clinical features**—LD encompasses several overlapping clinical phenotypes characterized by abnormal activity of the muscles of the larynx.\textsuperscript{126–129} The most common subtypes are adductor or abductor spasmodic dysphonia (SD), while less common subtypes include laryngeal breathing dystonia (also known as dystonic respiratory stridor)\textsuperscript{130–132} and singer’s dystonia.\textsuperscript{133} In SD, spasms of laryngeal muscles cause intermittent voice breaks. SD is a task-specific dystonia where spasms typically occur during speaking but abate with singing, shouting, crying or whispering. Adductor SD affects 90% of cases and is caused by overactivity of vocal fold adductors, with intermittent hyperadduction leading to an intermittently strained and strangled voice. Spasms tend to occur with vowels, particularly during glottal stops between vowels. Rarely, adductor and abductor SD occur together.

LD may occur with vocal tremor, which is characterized by more regular oscillations of multiple laryngeal muscles.\textsuperscript{129, 134, 135} SD and tremor may be difficult to discriminate because apparently regular voice breaks in SD may resemble the rhythmic oscillations of tremor. LD is readily confused with another disorder, muscle tension dysphonia (MTD), where there is a general constriction of multiple laryngeal muscles leading to a strained voice that does not vary with different parts of speech.\textsuperscript{136–138} Isolated MTD has many features atypical for dystonia and can be reversed with voice therapy. However, many patients with LD may have features of MTD, and the exact relationship between LD and MTD remains unclear. MTD may not be a manifestation of dystonia, but rather a behavioral compensation for voice weakness or instability.

Uncertainties regarding diagnostic criteria and distinctions among the subtypes of LD are important challenges.\textsuperscript{128} SD and other forms of LD are poorly recognized by providers not familiar with the disorder, in part because of the lack of diagnostic criteria. In addition, there are no validated severity scales for LD.

**Etiology and pathogenesis**—The etiology and pathogenesis of LD is heterogeneous.\textsuperscript{128} Several observations point to a genetic contribution, although no genes responsible for isolated LD have been found. LD may be a particularly prominent or isolated manifestation of mutations more commonly associated with generalized dystonia, especially the \textit{THAP1} gene.\textsuperscript{139, 140} Recently, mutations in the \textit{TUBB4a} gene have emerged as a potential cause in some families where generalized dystonia includes prominent laryngeal and lingual dystonia.\textsuperscript{141–143} The “whispering dysphonia” in these patients is atypical for sporadic SD and may reflect a compensatory adaptation to laryngeal spasms. These families emphasize the importance of phenotypic subtypes within LD. There also is strong epidemiological evidence for non-genetic contributions. Many patients report developing LD following an upper respiratory infection, laryngeal trauma, exposure to a neuroleptic, or periods of high stress.\textsuperscript{129, 144, 145}

The neuroanatomical basis for LD also remains an open question. Any model for pathogenesis should account for difficulties with speaking while sparing closely related tasks of singing, whispering, shouting and crying. PET studies have revealed both increases and decreases in blood flow to several regions of the cerebral cortex in adductor SD.\textsuperscript{146} Studies involving fMRI during symptomatic and asymptomatic tasks also have pointed to abnormal activation of the cerebral cortex and cerebellum,\textsuperscript{147, 148} while diffusion tensor

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imaging (DTI) has revealed white matter defects in or near the basal ganglia, cerebellum and thalamus. A VBM study revealed changes in cerebral cortex and cerebellum.

**Treatment challenges**—Botulinum toxins are routinely used for treating adductor SD, despite frequent transient adverse effects such as vocal weakness, breathiness, and choking with liquids. Satisfactory responses are more difficult to achieve in abductor SD. There is only one small, single-site, double-blinded study of botulinum toxins for adductor SD, but none for other forms of LD.

Several different surgical approaches also are offered to patients with SD including myectomy targeting the thyroarytenoids, thyroplasty to alter the cartilaginous structure of the larynx, or denervation-reinnervation procedures that cut branches of the recurrent laryngeal nerve to the thyroarytenoid muscles and suture the stump to the ansa cervicalis. However, there are no controlled trials addressing safety and efficacy for these procedures.

**Limb dystonias**

**Clinical features**—Isolated limb dystonia can occur in adults, most commonly an upper limb. Most are task-specific, where the limb has been used for a repetitive activity for long periods. Dystonia can arise with virtually any task. Dystonia may remain task-specific, or it may lose specificity over time. One common form is writer’s cramp. Another is musician’s dystonia among patients who play wind or string instruments, or piano. Similar to other AOFD, tremor is common and may predominate. Isolated leg dystonias are less common in adults. They may be sporadic, or associated with repetitive activities such running marathons. Leg dystonia may also be a presenting manifestation of Parkinson disease, emerging before tremor an bradykinesia become apparent.

In addition to repetitive activity, there may be a history of trauma. A controversial entity is the complex regional pain syndrome (CRPS), where approximately half of the patients have relatively fixed dystonic postures. Patients with fixed dystonia are more likely to be psychogenic, and many CRPS cases may be psychogenic.

**Etiology and pathogenesis**—The cause of most limb dystonias is multifactorial, with environmental factors of repetitive activity and trauma interacting with an inherent predisposition. One predisposing substrate may be a loss of inhibitory processes in the nervous system, along with abnormal plasticity. Another important factor is the interaction between the task and the mechanical ability of the limb. If the demand exceeds the ability, compensatory adaptations may result in abnormal motor behavior. This is particularly important in musicians where task demands may be extreme.

Imaging studies have pointed to different brain regions underlying focal hand dystonias. In VBM studies, one frequent finding is an abnormality in the hand area of the sensorimotor cortex. In fMRI studies, there frequently are increases in activity of the sensorimotor cortex and decreases in the supplementary motor area, but there also are changes in basal ganglia and cerebellum.

**Treatment challenges**—Oral drugs are seldom of value. Botulinum toxin injections are useful, but results are variable because of the complex patterns of hand movements, the numbers of muscles sometimes involved, and difficulties in discriminating abnormal movements from compensations. Deciding where and how much to inject can be challenging, particularly in musicians where there is a need for exquisitely good motor control.
Various forms of occupational therapy are reported to be of benefit in small but usually uncontrolled trials.\textsuperscript{166, 167} Results are inconsistent and short-lived, so these methods are not widely used. Limb dystonias respond well to DBS of the globus pallidus. Additionally, there reports of success with thalamotomy or thalamic DBS, a target not often used for other dystonias.\textsuperscript{168} Whether this means the ideal target for limb dystonias is different from other dystonias is not known.

Less well-studied AOFD

**Oromandibular dystonia (OMD)—**Dystonic movements may be limited to lower facial muscles, jaw, or tongue. These regions may be affected in isolation or together. When they occur together with BL, the combination is sometimes called Brueghel or Meige syndrome, although these eponyms have been questioned.\textsuperscript{169}

Involvement of the lower face causes grimacing, lip pursing, and other facial contortions. Involvement of jaw muscles leads to sustained, repetitive or action-induced jaw opening or closing, protrusion or retraction, or deviation. Symmetric contractions of jaw closers (medial pterygoids, masseters and temporalis muscles) leads to jaw closing dystonia or dystonic bruxism. Symmetric contraction of jaw openers (lateral pterygoids and digastrics) leads to jaw opening or protrusion. Asymmetric contraction of openers or closers leads to lateral deviations.\textsuperscript{170} In addition, simultaneous or alternating movements of openers and closers may result in jaw tremor.\textsuperscript{171}

Tongue movements can be sustained, episodic, or action-induced.\textsuperscript{172–176} Lingual dystonia may be isolated and idiopathic,\textsuperscript{90, 177, 178} or a feature of a more complex dystonia syndrome.\textsuperscript{179}

OMD often is aggravated by talking or chewing, causing disability related to speaking or eating, and sometimes causing serious weight loss.\textsuperscript{180, 181} Jaw pain can be prominent, leading to misdiagnosis as the temporomandibular joint syndrome.\textsuperscript{182} Musicians who play wind instruments may develop embouchure dystonia involving lip, jaw, and tongue muscles.\textsuperscript{183} It presumably occurs because of repetitive practice, but may spread to involve activities besides music. OMD sometimes follows dental work, although a causal relationship has not been established.

OMD does not respond well to oral medications. Some cases respond to botulinum toxins, but treatment outcomes seem less predictable than other focal dystonias.

**Axial dystonia—**Axial dystonia, apart from the neck, is uncommon in adults.\textsuperscript{184} Truncal dystonia may occur in isolation, or as a feature of Parkinson’s disease and related conditions.\textsuperscript{185} Patients may bend forward (camptocormia), backwards (opisthotonus), or sideways (Pisa syndrome). Movements can be fixed or spasmodic. Dystonia is not the cause for all abnormal truncal postures. For example, scoliosis may be a manifestation of truncal dystonia, but scoliosis also may have other causes.\textsuperscript{186, 187} Exposure to dopamine receptor antagonists may lead to truncal dystonia, where bending is more often backwards.\textsuperscript{44}

Treatment with oral medications usually is ineffective. Botulinum toxin injections into the paraspinal and abdominal muscles may help, but results usually are modest because of broad involvement of large truncal muscles.\textsuperscript{188, 189} Excellent results have been reported with DBS,\textsuperscript{190} but few patients have been studied.
FOCAL DYSTONIAS: TO LUMP OR SPLIT?

The case for splitting

The preceding summary highlights obvious differences in the overt clinical features of the AOFD. Even within the major subtypes there are distinct phenotypes for each, with important treatment implications. In addition to differences in clinical manifestations, other differences are clear from epidemiological studies. For example, most AOFD are more common in women than men, except for limb dystonias (Table 1). AOFD also differ in age at onset. A meta-analysis encompassing 5057 patients across 83 different studies \(^{191}\) revealed significant differences in mean age at onset for writer’s cramp (38.4 years), CD (40.8 years), SD (43.0 years) and BL/OMD (55.7 years). The risk of spread also varies. \(^{192, 193}\) BL is the most likely to spread, with approximately 50% risk of spread beyond the orbicularis oculi over 5 years. In comparison, for CD and SD the risk of spread is only 15% over 5 years. Another difference among the AOFD is that some emerge only with specific tasks, while others lack obvious task specificity. \(^{156, 194–196}\) Finally, there are different epidemiological associations such as trauma for CD, dry eye for BL, laryngitis for LD, and repetitive use for limb dystonias.

There also are important etiological differences among the AOFD. These differences are most obvious for inherited AOFD, where some genes are linked preferentially with one subtype. \(^{49, 197}\) These many differences lead to obvious questions regarding why AOFD are lumped together as a group.

The case for lumping

**Shared genes**—Historically, many AOFD were considered to be distinct entities under the category of “occupational cramps” or spasms. In 1976 Marsden proposed grouping them as “formes fruste” of generalized dystonia. \(^{198}\) The evidence for combining them included observations that AOFD phenotypically resemble more generalized dystonias, observations that one AOFD sometimes spreads to include another, and observations that patients with one AOFD often had family members with different AOFD. A review of published reports of 13 families revealed 5 with a single type of AOFD, suggesting a familial influence for specific types. \(^{8}\) However, 8 families had multiple different types of AOFD, suggesting a common influence for different subtypes. A combined analysis of 4 families where first degree relatives were examined directly suggested 54% had concordant phenotypes while 46% had mixed or discordant phenotypes. \(^{8}\) These discordant families provide indirect evidence for shared etiological factors. \(^{8}\)

More direct evidence for genetic factors comes from genes responsible for early-onset generalized dystonias. The common GAG deletion in \(TOR1A\) responsible for generalized DYT1 dystonia may be associated with a phenotype resembling AOFD. A survey of 3216 patients in 17 studies of \(TOR1A\) mutations listed 21 cases with non-generalized syndromes including focal, segmental and multifocal patterns. \(^{33}\) Another study with 3028 patients across 17 studies listed 25 cases with non-generalized syndromes. \(^{34}\)

AOFD are more frequently associated with the \(THAP1\) gene, where the classical phenotype is generalized dystonia that begins in the neck or arm during adolescence or early adulthood. \(^{139}\) A review of 106 cases revealed 19 (18%) with focal and 30 (28%) with segmental distributions. \(^{199}\) Another review of 130 published cases revealed 21 (16.2%) with focal and 45 (34.6%) with segmental distributions. \(^{35}\)

A similar overlap among AOFD is evident for the newly discovered genes. \(GNAL\) mutations were associated with CD, BL, LD, and limb dystonia. \(^{37, 38}\) \(ANO3\) mutations were associated with CD, but several cases also had LD or limb dystonia. \(^{39}\)
Shared molecular and cellular pathways—At present, delineating shared pathways for AOFD is challenging because only a few genes are known. These genes play roles in different molecular and cellular pathways. The TOR1A gene encodes a molecular chaperone, THAP1 a transcription factor, CIZ1 a DNA replication enzyme, ANO3 an ion channel, TUBB4a a microtubule-associated protein, and GNAL a G-protein involved in intracellular signaling. It is not yet clear how, or if, these pathways intersect.

However, several shared pathways have been recognized among the many different mixed dystonia syndromes where many causes have been identified. One of the earliest themes recognized involves dopamine signaling. Dystonia is a feature of several inherited defects that affect dopamine synthesis directly such as DOPA-responsive dystonia, or indirectly, such as Lesch-Nyhan disease. The dopamine theme is not limited to inherited defects, since drugs that block dopamine transmission can induce acute dystonic reactions or tardive dystonia in the absence of a genetic defect. Many patients with early-onset Parkinson’s disease present with dystonia of one limb as the dominant clinical feature. Imaging and postmortem studies also have revealed subtle abnormalities of dopamine systems in both inherited and sporadic primary dystonias. Defects in dopamine signaling also are linked with dystonia in animal models. These observations suggest that dysfunction of dopamine signaling is a shared theme for several types of dystonia.

Another shared theme identified via studies of animals with drug-induced or inherited dystonia involves defects in ion channels. Inherited defects in the CACNA1A gene that encodes a calcium channel have been linked with a variety of neurological disorders in humans, including CD and writer’s cramp. Defects in the KCNMA1 gene encoding a potassium channel underlie some paroxysmal dyskinesias, where dystonia may be a prominent feature. The ANO3 gene described above is thought to encode a calcium-activated chloride channel.

Another shared molecular theme involves mitochondrial dysfunction. Dystonia occurs in mitochondrial disorders such as Leber’s optic neuropathy, Leigh’s syndrome, and the Mohr-Tranebjærg dystonia-deafness syndrome. In some cases, dystonia can be the dominant neurological problem. In other cases it may be limited to focal or segmental patterns. The mitochondrial theme is not restricted to inherited defects. Dystonia occurs among children and non-human primates exposed to the 3-nitropropionic acid, a mitochondrial poison. Mitochondrial defects also have been associated with sporadic AOFD.

Shared anatomical circuitry—Historically, dystonia has been attributed to dysfunction of the basal ganglia. The evidence supporting a role for the basal ganglia is strong and has been reviewed several times. However, there has been increasing appreciation that other brain regions also may be involved, particularly the cerebellum. These studies also have been reviewed. Dystonia now is viewed as a disorder where the basal ganglia play a role as one node in a broader network that includes the cerebellum and other regions.

Certain subtypes of dystonia may share a causal pathology in the basal ganglia, while others may arise primarily from dysfunction of the cerebellum. It also is possible that combined dysfunction of two nodes is related to the expression of dystonia, the “two hit hypothesis”. Alternatively, dystonia may arise from defective communication among different nodes in the network. Although more work needs to be done to determine which of these models for anatomical pathogenesis is most appropriate for different
subtypes of dystonia, it is clear that there is a shared anatomical network for many types of dystonia.

**Shared physiological substrates**—Three common themes have arisen from physiological studies. The first theme involves loss of inhibitory processes, which have been found in different types of dystonia and at multiple levels of the neuraxis including the spinal cord, brainstem, and cortex.

The second theme involves defects in sensorimotor integration. Although patients with AOFD do not have overt sensory deficits, they have consistently higher spatial and temporal somatosensory discrimination thresholds. Altered sensory thresholds have been reported for many types of dystonia, and can be measured in both affected and unaffected body parts, even among unaffected family members in large pedigrees where other members are affected.

The third theme involves maladaptive neural plasticity, which also has been reported for many different types of dystonia. It is striking that these three themes have arisen so many times across different types of dystonia including the AOFD, inherited generalized syndromes, and acquired dystonias. These observations support the concept that AOFD share certain physiological defects.

**A conceptual model for lumpers & splitters**

The differences and similarities among AOFD can be accommodated by a conceptual model that focuses on different biological levels. Like other disorders, the pathogenesis of dystonia can be viewed as a multi-step process where some original insult triggers a series of abnormalities at the molecular, cellular, anatomical, and physiological levels (Figure 1A). While there may be many different triggers, specific subgroups of dystonia may share some downstream mechanisms of pathogenesis. Interactions among molecular and cellular pathways may occur for specific subgroups of dystonia (Figure 1B), but it seems naïve to assume that all will intersect at one common molecular pathway. Instead, pathogenesis may converge at the systems level, by affecting the same brain region, or by causing the same physiological substrate (Figure 1C–D). This model for pathogenesis can be constructed for some themes in dystonia, such as dopaminergic dysfunction and basal ganglia defects (Figure 2). Further studies are needed to understand how other dystonias should be grouped.

This model has important implications for experimental therapeutics. Interventions targeting “upstream” pathways may be useful for preventing the cascade of events that leads to specific types of dystonia, such as targeting the TOR1A gene by RNAi for DYT1 dystonia. However, this intervention seems unlikely to have any therapeutic impact on other forms of dystonia that do not involve this molecular pathway. On the other hand, targeting “downstream” pathways may be useful for interrupting the cascade of events in broader groups of dystonias. For example, DBS of the globus pallidus has proven effective for many etiologically unrelated forms of dystonia, most likely because it alters common signaling pathways. The botulinum toxins are effective in an even broader group of unrelated dystonias, because they target the final common defect involving overactive muscles.

**FUTURE PROSPECTS**

In the past few years, there have been enormous strides in delineating the many clinical manifestations of dystonia, discovering underlying etiologies, and elucidating mechanisms of pathogenesis. At the same time, many new questions have arisen. This section summarizes some of the important unsolved questions, organized according to different
Clinical research

Historically, there has been a tendency to lump different AOFD together for studies. This strategy has been helpful for increasing sample sizes, but underlying etiological heterogeneity may introduce unknown variables and thereby mask findings relevant to specific subtypes. Until these variables are better understood, it seems safer to study phenotypically homogeneous or etiologically defined patient populations separately, before combining data across groups. Detailed clinical information therefore is essential for generating defined populations for studies. Merely listing cases as having one of the AOFD no longer seems sufficient.

There also are a number of other important clinical issues to address. The relationship between dystonia and tremor has become increasingly murky. The nosological relationships between dystonia and several related disorders also needs attention. Some examples include athetosis, mirror movements, “apraxia” of eyelid opening, MTD, paroxysmal dyskinesias, and pseudo-dystonia. The significance of non-motor features and impact on quality of life also needs to be explored, as there is growing suspicion that they may have greater impact than the movement disorder itself.

Finally, there seems a need for better awareness of the many clinical manifestations of dystonia. Although dystonia is readily recognized by experts in movement disorders, there is poor recognition among primary care givers and general neurologists with several years often elapsing between symptom onset and diagnosis.

Molecular & cellular basis

While several genes for AOFD recently have been reported, there are many more families for which genes are not yet known, and even more sporadic cases where genetic contributions are an open question. The relevance of the newly discovered genes to broader populations also must be explored by examining large numbers of AOFD. The identification of additional genes is important, as it may facilitate diagnostic testing and identification of shared pathways that can become the targets of rational drug design.

While many genes responsible for mixed dystonia syndromes often are fully penetrant, all genes so far discovered for isolated dystonia syndromes appear to be partially penetrant. The partial penetrance may suggest dystonia is a polygenic disorder or one that requires an additional environmental trigger. The mechanisms of partial penetrance have so far received little attention, yet seem important for providing clues to pathogenesis.

Anatomical circuitry

Recent information has led to a shift in thinking away from the basal ganglia as the sole cause of dystonia to a network model that includes other motor systems. This shift has raised numerous questions for research. Exactly which regions of the network are most important and how the network is disrupted to cause dystonia remain to be determined.

Two major challenges emerged from recent reviews of imaging studies in dystonia. One is a lack of consistent findings across studies. While some inconsistencies may reflect differences among AOFD or imaging methods, there are inconsistencies even within a single imaging modality of the same AOFD. For example, many studies identify the basal ganglia as being abnormal in CD, but different subregions are affected in different studies, occasionally with opposing changes in the same brain region using the same imaging...
Resolving these inconsistencies is important for establishing reliability and may facilitate recognition of common patterns in different AOFD.

Another major challenge is that imaging studies are correlational, and it is difficult to discriminate which brain abnormalities cause dystonia from those that reflect secondary adaptations. Motor pathways of the brain are interconnected, so abnormalities in one region influence another. A related difficulty is that movement itself changes the brain. Highly trained individuals, such as musicians and golfers, normally develop changes in brain structure and function that can be measured by modern imaging methods. Even non-professionals show measurable changes when learning how to juggle over a period as short as one week. These observations raise concern that many abnormalities observed in imaging studies might not be the cause of dystonia, but rather a consequence of the abnormal movements. There are similar concerns regarding the secondary effects of sensory feedback on brain structure and function. Disentangling cause from effect in dystonia will require the application of novel strategies.

Additional histopathological studies are needed to further explore recent findings of subtle abnormalities among cerebellar Purkinje neurons in patients with CD. Studies in animal models may reveal anomalies that can be subsequent targets of human investigations. Animal models also may be valuable in testing hypotheses regarding cause and effect. Unfortunately, while there are many animal models for generalized dystonias, there are few for AOFD. There are no accepted animal models for LD. There is one rat model for BL. Animal models also may be valuable in testing hypotheses regarding cause and effect. Unfortunately, while there are many animal models for generalized dystonias, there are few for AOFD. There are no accepted animal models for LD. There is one rat model for BL. For CD, some rodent or primate models have been proposed. However, few of these models have been replicated by more than one laboratory, and none have been adequately validated. Developing and validating animal models for AOFD remains a high priority. Until better AOFD models are developed, insights from animal studies must rely on extrapolations of results from models of generalized dystonias.

Additional histopathological studies are needed to further explore recent findings of subtle abnormalities among cerebellar Purkinje neurons in patients with CD. Studies in animal models may reveal anomalies that can be subsequent targets of human investigations. Animal models also may be valuable in testing hypotheses regarding cause and effect. Unfortunately, while there are many animal models for generalized dystonias, there are few for AOFD. There are no accepted animal models for LD. There is one rat model for BL. For CD, some rodent or primate models have been proposed. However, few of these models have been replicated by more than one laboratory, and none have been adequately validated. Developing and validating animal models for AOFD remains a high priority. Until better AOFD models are developed, insights from animal studies must rely on extrapolations of results from models of generalized dystonias.

Human & animal physiology

Physiological studies of humans repeatedly have identified three common themes of loss of inhibition, abnormal sensorimotor integration, and maladaptive plasticity. How these themes may be linked remains unclear. While these defects have been attributed to dysfunction of the basal ganglia, direct evidence for the responsible anatomical circuitry is lacking, and the possibility that they arise instead from dysfunction of the cerebellum has been raised.

Evidence that these physiological defects play a causal role in dystonia also is lacking, and the possibility remains that some may be secondary to the movement disorder instead. Two related pieces of evidence have been cited as evidence for causality. One is that these abnormalities can be detected for body regions unaffected by dystonia, and the other is that they can be detected from both sides of the brain, even when symptoms are unilateral. These findings may imply a predisposing endophenotype. However, it is widely known that “unaffected” body regions are often not normal in dystonic patients, and physiological stimuli applied to one side of the body can be detected on both sides of the brain. Additionally, the occurrence of some physiological abnormalities in psychogenic dystonia supports the view that they may not be causal. Thus further direct evidence for a causal role seems important to establish. Here again, animal models could be valuable in discriminating cause from consequence.

Sensory tricks also appear to be common among many of the AOFD, and their clinical features have been characterized in detail. However, the physiological mechanisms
responsible for their effectiveness has received less attention, and may provide clues towards pathogenesis.

**Clinical trials & experimental therapeutics**

Discoveries from basic sciences have pointed to some novel targets for rational drug development. Several drug-screening assays have been devised.\(^{277, 278}\) Additionally, there are several small animal models suitable for empirical testing of drugs.\(^{267}\) These models also have been used to identify promising new agents. There is additional interest in the possibility of using drugs that suppress dyskinesias in Parkinson’s disease, because some dyskinesias have a dystonic quality.\(^{279}\)

Clinical studies and trials require validated measurement tools that are sensitive to severity. Several rating scales have been used for years, but each has some limitations.\(^{280, 281}\) Validated rating scales are lacking for some AOFD, and none have been validated for children. In addition, there is increased appreciation for the impact of non-motor features, but how they relate to overall quality of life remains unexplored.\(^{282–284}\)

A major barrier in testing candidate drugs in clinical trials is limited experience with trial designs in dystonia. Effective designs have been developed for trials involving botulinum toxins\(^{13, 66}\) or DBS,\(^{285, 286}\) but there are no widely accepted designs for drugs. Large, double-blinded, placebo-controlled trials present challenges for rare diseases, and they are financially unattractive to industry. Similar to Parkinson’s disease, it is likely that trial designs for symptomatic therapies will differ from those of disease-modifying therapies. Finally, any trial in AOFD must incorporate a means for addressing the cyclical swings in severity associated with treatment with botulinum toxins. Addressing these issues will be important for translating the many novel scientific discoveries and candidate drugs into meaningful new treatments for AOFD.

**Acknowledgments**

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**BIBLIOGRAPHY**


73. Waln O, Ledoux MS. Blepharospasm plus cervical dystonia with predominant anterocollis: A distinctive subphenotype of segmental cranio cervical dystonia? Tremor Other Hyperkinet Mov. 2011; 2011(1)


241. Lehericy S. A current view of the anatomic basis of dystonia. Mov Disord. 2013 This issue.
258. Zoons E, Tijssen MAJ. Pathological changes in the brain in cervical dystonia pre- and post-mortem: a commentary with a special focus on the cerebellum. Exp Neurol. in press.


Mov Disord. Author manuscript; available in PMC 2014 June 15.


Figure 1.
Conceptual model for similarities and differences among different dystonias. A simplified scheme for pathogenesis begins with a specific etiology and proceeds through a series of downstream processes in the pathogenesis of dystonia (A). Etiologically different types of dystonia may share a similar molecular pathway and similar subsequent pathogenesis (B). Alternatively, etiologically different types of dystonia may differ at the molecular level, yet disrupt the same neuronal population (C). Etiologically different types of dystonia instead may disrupt a common anatomical circuit (D). Ultimately, all may share some similar biological defect at the systems level to result in the patterns of muscle activity that define dystonia.
Figure 2.
Example model for shared mechanisms of pathogenesis at different biological levels. A simplified scheme for pathogenesis begins with a specific etiology and proceeds through a series of downstream processes in the pathogenesis of dystonia (A). Some disorders are known to disrupt a common molecular pathway involving dopamine synthesis via different molecular mechanisms (B). Two gene defects (GCH1 and PTPS) affect dopamine synthesis by disrupting biopterin metabolism, while two other gene defects (TH and AADC) affect other steps in dopamine synthesis. All 4 of these disorders disrupt nigrostriatal dopamine neuron function, signaling in basal ganglia circuits, and alter systems physiology to produce dystonia. Nigrostriatal dopamine neurons may be affected via other genetic mechanisms (C: HPRT) or exposure to dopamine receptor antagonists (D) to cause dystonia. Damage may also occur to basal ganglia circuits more directly, as in some mitochondrial disorders, glutaric aciduria, biotin-responsive basal ganglia disease, 3-nitropropionic acid exposure (E).
### Table 1

**Sex Differences Among Adult-Onset Focal Dystonias**

<table>
<thead>
<tr>
<th>Focal dystonia</th>
<th>Total cases</th>
<th>F:M ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>2634</td>
<td>1.5</td>
</tr>
<tr>
<td>SD</td>
<td>1411</td>
<td>2.0</td>
</tr>
<tr>
<td>BL</td>
<td>739</td>
<td>2.0</td>
</tr>
<tr>
<td>UL</td>
<td>296</td>
<td>0.6</td>
</tr>
<tr>
<td>OMD</td>
<td>37</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Data for this table were pooled from published reports that focused specifically on sex differences. The ratio of females to males (F:M ratio) was calculated as a weighted average of all cases.
Table 2

Familial Clustering of Adult-Onset Focal Dystonias

<table>
<thead>
<tr>
<th>Source</th>
<th>Type of dystonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhidayasiri et al, 2005^291</td>
<td>UL</td>
</tr>
<tr>
<td>Brancati et al, 2002^292</td>
<td>BL, CD, UL</td>
</tr>
<tr>
<td>Bressman et al, 1996 (A)^293</td>
<td>CD, UL</td>
</tr>
<tr>
<td>Bressman et al, 1996 (B)^293</td>
<td>CD</td>
</tr>
<tr>
<td>Cassetta et al, 1999^294</td>
<td>BL, CD OMD</td>
</tr>
<tr>
<td>Defazio et al, 2003a (1)^295</td>
<td>BL</td>
</tr>
<tr>
<td>Defazio et al, 2003a (2)^295</td>
<td>BL</td>
</tr>
<tr>
<td>Defazio et al, 2003b (3)^296</td>
<td>BL, CD</td>
</tr>
<tr>
<td>Defazio et al, 2003b (4)^296</td>
<td>BL</td>
</tr>
<tr>
<td>Defazio et al, 2003b (5)^296</td>
<td>CD, UL</td>
</tr>
<tr>
<td>Defazio et al, 2003b (6)^296</td>
<td>BL, UL</td>
</tr>
<tr>
<td>Defazio et al, 2003b (10)^296</td>
<td>BL, CD, OMD</td>
</tr>
<tr>
<td>Gasser et al, 1998^297</td>
<td>UL</td>
</tr>
<tr>
<td>Jimenez-Jimenez et al, 2002^298</td>
<td>BL, CD, OMD</td>
</tr>
<tr>
<td>Leube et al, 1996^299</td>
<td>CD, LD, UL</td>
</tr>
<tr>
<td>Leube et al, 1997^32</td>
<td>CD, LD, UL</td>
</tr>
<tr>
<td>Micheli et al, 1994^100</td>
<td>CD, UL</td>
</tr>
<tr>
<td>Munchau et al, 2006^301</td>
<td>BL, CD, UL, OMD</td>
</tr>
<tr>
<td>Norgren et al, 2011^302</td>
<td>BL, CD, G, S, UL</td>
</tr>
<tr>
<td>O’Riordan et al, 2004^196</td>
<td>CD, UL</td>
</tr>
<tr>
<td>Puschmann et al, 2011^303</td>
<td>BL, CD, OMD, LL, UL</td>
</tr>
<tr>
<td>Schmidt et al, 2006 (A)^304</td>
<td>UL</td>
</tr>
<tr>
<td>Schmidt et al, 2006 (B)^304</td>
<td>UL</td>
</tr>
<tr>
<td>Schmidt et al, 2006 (C)^304</td>
<td>UL</td>
</tr>
<tr>
<td>Uitti et al, 1993^305</td>
<td>CD</td>
</tr>
<tr>
<td>Winter et al, 2012^306</td>
<td>BL, CD, LD, OMD, UL</td>
</tr>
</tbody>
</table>

This table was modified and extended from a prior review.\(^8\) It includes individual families with AOFD with at least 3 affected and subjects were directly examined. In some cases, clinical details were limited and only presenting features were provided. Reports containing more than one family show families separately.

In other Abbreviations: BL=blepharospasm; CD=cervical dystonia; G=generalized; LD=laryngeal dystonia; OMD=oromandibular dystonia; S=segmental; UL=upper limb dystonia.
**Table 3**

**THAP1 Sequence Variants & Focal Dystonias**

<table>
<thead>
<tr>
<th>Source</th>
<th>Total cases</th>
<th>Focal dystonias</th>
<th>Type(s) of focal dystonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blanchard et al, 2011</td>
<td>178</td>
<td>1</td>
<td>CD/UL (1)</td>
</tr>
<tr>
<td>Bonetti et al, 2009</td>
<td>158</td>
<td>1</td>
<td>CD/FHD(1)</td>
</tr>
<tr>
<td>Bressman et al, 2009</td>
<td>104</td>
<td>5</td>
<td>FHD(4), LD(1)</td>
</tr>
<tr>
<td>Cheng et al, 2011</td>
<td>111</td>
<td>2</td>
<td>CFD/CD(1), CFD/CD/LD (1)</td>
</tr>
<tr>
<td>Cheng et al, 2012</td>
<td>102</td>
<td>7</td>
<td>CD(2), CD/BL(2), CD/BL/trunk(1), CD/OMD(1), CD/trunk(1)</td>
</tr>
<tr>
<td>Clot et al, 2010</td>
<td>113</td>
<td>2</td>
<td>CD(1), CFD/CD/LD/UE(1)</td>
</tr>
<tr>
<td>Djarmati et al, 2009</td>
<td>320</td>
<td>2</td>
<td>CD/FHD(2)</td>
</tr>
<tr>
<td>Dobricic et al, 2012</td>
<td>281</td>
<td>4</td>
<td>UL(1), LD(1), CD/LD(1), CD/UL(1)</td>
</tr>
<tr>
<td>Fuchs et al, 2009</td>
<td>180</td>
<td>11</td>
<td>UL(4), LD(1), UL/LL(1), CD/UL(2), OMD/CFD(1), LD/CD/CFD(1) CFD/OMD(1)</td>
</tr>
<tr>
<td>Groen et al, 2010</td>
<td>455</td>
<td>4</td>
<td>CD(1), OMD/UE/CD(1), OMD/UE/CD/LD (1), CD/UE/Trunk(1)</td>
</tr>
<tr>
<td>Groen et al, 2011</td>
<td>109</td>
<td>1</td>
<td>LD/OMD(1)</td>
</tr>
<tr>
<td>Houlden et al, 2010</td>
<td>390</td>
<td>5</td>
<td>CFD/OMD(1), CD/UL (3), OMD/UL(1)</td>
</tr>
<tr>
<td>LeDoux et al, 2012</td>
<td>750</td>
<td>3</td>
<td>CD/UL(1), SD/CD/UL/CFD/OMD(2)</td>
</tr>
<tr>
<td>Lohmann et al, 2012</td>
<td>567</td>
<td>3</td>
<td>CD(1), UL+S(2)</td>
</tr>
<tr>
<td>Paison-Ruiz et al, 2009</td>
<td>24</td>
<td>2</td>
<td>UL/LL(1), UL/CFD(1)</td>
</tr>
<tr>
<td>Prudente et al, 2013</td>
<td>6</td>
<td>4</td>
<td>CD(2), CD/BL(1), CD/BL/FD(1)</td>
</tr>
<tr>
<td>Sohn et al, 2010</td>
<td>610</td>
<td>5</td>
<td>CD (4), CD/OMD/LD (1)</td>
</tr>
<tr>
<td>Song et al, 2011</td>
<td>231</td>
<td>2</td>
<td>CD(1), CD/trunk (1)</td>
</tr>
<tr>
<td>Van Gerpen et al, 2010</td>
<td>1</td>
<td>1</td>
<td>UL/LL(1)</td>
</tr>
<tr>
<td>Xiao et al, 2010</td>
<td>1114</td>
<td>17</td>
<td>CD(6), LD(5), BL(2), OMD(1), UL(1), BL/LD/CFD(1), UL/CD/OMD(1)</td>
</tr>
<tr>
<td>Xiromerisiou et al, 2012</td>
<td>150</td>
<td>1</td>
<td>CD(1)</td>
</tr>
</tbody>
</table>

This table includes a summary of THAP1 sequence variants among patients with primary dystonia, where focal or segmental patterns were found. The distributions were inferred from information provided in the original reports, which sometimes was limited. The numbers in parentheses indicate the numbers of cases for type. In many cases, the pathogenicity of the sequence variant has not been established.

Abbreviations: BL=blepharospasm; CD=cervical dystonia; CFD=craniofacial dystonia; LD=laryngeal dystonia; LL=lower limb dystonia; OMD=oromandibular dystonia; S=segmental dystonia (regions not specified); UL=upper limb dystonia.
## Table 4

### Research Priorities for AOFD

<table>
<thead>
<tr>
<th>Research discipline</th>
<th>Research priorities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular &amp; cellular</td>
<td>Identify novel genes</td>
</tr>
<tr>
<td></td>
<td>Elucidate shared molecular pathways</td>
</tr>
<tr>
<td></td>
<td>Develop cell models to study molecular pathogenesis</td>
</tr>
<tr>
<td></td>
<td>Develop animal models to study pathogenesis</td>
</tr>
<tr>
<td>Anatomical</td>
<td>Distinguish cause from consequence</td>
</tr>
<tr>
<td></td>
<td>Elucidate reasons for inconsistent findings</td>
</tr>
<tr>
<td></td>
<td>Utilize animal models for understanding circuitry</td>
</tr>
<tr>
<td></td>
<td>Conduct more precise autopsy studies</td>
</tr>
<tr>
<td>Physiological</td>
<td>Distinguish cause from consequence</td>
</tr>
<tr>
<td></td>
<td>Explore molecular and anatomical basis</td>
</tr>
<tr>
<td></td>
<td>Explore physiological mechanisms of sensory tricks</td>
</tr>
<tr>
<td></td>
<td>Utilize animal models for understanding circuitry</td>
</tr>
<tr>
<td>Clinical research</td>
<td>Refine appreciation of clinical subtypes</td>
</tr>
<tr>
<td></td>
<td>Explore relationship to tremor</td>
</tr>
<tr>
<td></td>
<td>Explore relevance of non-motor features</td>
</tr>
<tr>
<td></td>
<td>Improve education and awareness</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>Refine or develop rating scales</td>
</tr>
<tr>
<td></td>
<td>Develop trial designs for novel drugs</td>
</tr>
<tr>
<td></td>
<td>Conduct trials of recently discovered agents</td>
</tr>
</tbody>
</table>

This table provides partial a list of some of the important research questions in AOFD, listed according to research discipline rather than priority. These items were included on the basis of a series of workshops focused on delineating research priorities in each of the areas.