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Dystonia: Current Knowledge and Treatment

Research Priorities in Limb and Task-Specific Dystonias

Dystonia, which causes intermittent or sustained abnormal postures and movements, can present in a focal or a generalized manner. In the limbs, focal dystonia can occur in either the upper or lower limbs and may be task-specific causing abnormal motor performance for only a specific task, such as in writer's cramp, runner's dystonia, or musician's dystonia. Focal limb dystonia can be non-task-specific and may, in some circumstances, be associated with parkinsonian disorders. The true prevalence of focal limb dystonia is not known and is likely currently underestimated, leaving a knowledge gap and an opportunity for future research. The pathophysiology of focal limb dystonia shares some commonalities with other dystonias with a loss of inhibition in the central nervous system and a loss of the normal regulation of plasticity, called homeostatic plasticity. Functional imaging studies revealed abnormalities in several anatomical networks that involve the cortex, basal ganglia, and cerebellum. Further studies should focus on distinguishing cause from effect in both physiology and imaging studies to permit focus on most relevant biological correlates of dystonia. There is no specific therapy for the treatment of limb dystonia given the variability in presentation, but off-label botulinum toxin therapy is

Abbreviations: BOLD, blood oxygen level dependent; BoNT, botulinum neurotoxin; CSP, cortical silent period; DBS, deep brain stimulation; DMN, default more network; fMRI, functional magnetic resonance imaging; GPi, globus pallidus interna; LTP, long-term potentiation; M1, motor cortex; PAS, paired associative stimulation; PET, positron emission tomography; PMC, premotor cortex; RD, runner's dystonia; rTMS, repetitive transcranial magnetic stimulation; STDT, somatosensory temporal discrimination threshold; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

often applied to focal limb and task-specific dystonia. Various rehabilitation techniques have been applied and rehabilitation interventions may improve outcomes, but small sample size and lack of direct comparisons between methods to evaluate comparative efficacy limit conclusions. Finally, non-invasive and invasive therapeutic modalities have been explored in small studies with design limitations that do not yet clearly provide direction for larger clinical trials that could support new clinical therapies. Given these gaps in our clinical, pathophysiologic, and therapeutic knowledge, we have identified priorities for future research including: the development of diagnostic criteria for limb dystonia, more precise phenotypic characterization and innovative clinical trial design that considers clinical heterogeneity, and limited available number of participants.

Keywords: dystonia, limb, task-specific, research priorities, inhibition, deep brain stimulation, botulinum toxin

INTRODUCTION

The dystonias are a group of disorders characterized by sustained or intermittent muscle contractions causing abnormal and often repetitive movements, postures, or both (1, 2). Clinically the dystonias are classified according to the area of the body that is affected, their age at onset, temporal characteristics such as manner of onset or task specificity, and whether they are combined with other neurological or medical features. Etiologically, they are classified according to whether or not there is any associated brain pathology or evidence for a genetic basis. In this review, we will focus mainly on isolated limb dystonia that usually presents in adult life, most commonly is of unknown origin, and can be task-specific. We will summarize the current knowledge in the areas of clinical features, pathophysiology, as well as current therapeutic strategies. Then, we will identify priorities for future research based on the knowledge gaps revealed.

CLINICAL FEATURES

Dystonia of the Upper Limb

In epidemiological studies conducted in different parts of the world, the most commonly affected regions of the body include the neck and craniofacial areas (3, 4). The upper limbs are the third most commonly affected area, with estimated crude prevalence rates of approximately 5–70 cases per million (3, 4). The majority of upper limb dystonias first emerge in adulthood, with approximately 10–20% progressing to other body regions over 5–10 years (5–7). Upper limb dystonias less commonly emerge in children; although when they do present in children, there is greater risk of progression to generalized dystonia (8). The commonly reported features of upper limb dystonia include abnormal extension or flexion of the wrist or fingers, pain in the hand or forearm, and tremulous movements. Sometimes, there is pain in the hand or forearm, but this is typically not a prominent symptom and may be due to excessive muscular contraction.

In writer's cramp, a task-specific upper limb dystonia, patients initially report excessive tightness in hand or forearm muscles—sometimes described as a "cramp" (9). Even though there may be tightness, patients often can still perform the motor task, but over time, motor performance degrades with variable loss of dexterity, fatigue, or even pain. Abnormal postures can occur such as abnormal flexion or extension of the fingers and may be accompanied by abnormal wrist postures as well. It may not always be possible, however, to differentiate between abnormal posture as a manifestation of the dystonia and a compensatory contraction or movement. In this regard, voluntary movement of the contralateral (unaffected) hand may elicit the primary dystonic posture in the affected hand. This is "mirror dystonia," which refers to a phenomenon in which voluntary movements contralateral to the affected limb provoke dystonic movements on the affected side (10, 11). For instance, in writer's cramp when writing with the unaffected non-dominant hand, the normal voluntary movement can provoke or cause recapitulation of the dystonic movements in the affected hand, even though it is not engaged in the writing task. Assessing the abnormal posture in the affected hand brought out by "mirror dystonia" may be helpful in selecting the most appropriate muscles for botulinum toxin (BoNT) injection.

Writer's cramp has been described in the literature since 1830 and was originally classified as one of the "occupational neuroses" (12). Gowers may have been the first to recognize the aspect of "overuse" or repetitive action that typically precedes the development of the dystonic hand posture (12). He described that the abnormal spasm initially occurred only with writing, but later involved other actions—even affecting the non-dominant hand if used for writing (12). Given the relationship to repetitive action, writer's cramp must be differentiated from overuse syndromes and nerve entrapments (9). Sensory changes, in addition to pain and weakness, may be helpful in identifying peripheral nerve pathology rather than a dystonic etiology as a cause of the symptoms. In general, the remainder of the neurological exam should be normal in writer's cramp. If abnormalities are found, focal structural lesions as well as neurodegenerative causes of dystonia should be considered (**Table 1**).

Musician's dystonia of the hand and arm is a focal task-specific dystonia that classically affects performing artists at the peak of their careers with an average age of onset at 36 years of age (13). Musician's dystonia can also affect the embouchure. This unusual condition has afflicted famous musicians in the last two centuries, including Robert Schumann, Leon Fleisher, Gary Graffman, Peter Oundjian, and, likely, Yehudi Menuhin (14). Unlike all other forms of focal dystonia, musician's dystonia of the arm has a striking male to female predilection at 4:1 with prevalence

TABLE 1 | Limb dystonia by etiology.

Isolated: dystonia is the only motor feature	Adult-onset task-specific	• Writer's cramp • Musician's dystonia • Runner's dystonia
	Adult-onset non-task-specific limb dystonia	• Idiopathic
Combined: dystonia is combined with other movement disorders	Adult-onset non-task-specific limb dystonia	• Parkinson disease • Atypical parkinsonian disorder (i.e., corticobasal degeneration) • Posttraumatic or complex regional pain syndrome • Psychogenic
	Dystonia-plus syndromes	• Dopa-responsive dystonia • Rapid-onset dystonia parkinsonism • Myoclonus-dystonia syndrome
	Paroxysmal dyskinesia and dystonia	• Paroxysmal kinesigenic dystonia • Paroxysmal non-kinesigenic dystonia • Paroxysmal exercise-induced dystonia
	Heredodegenerative dystonia	• Wilson's disease • Huntington's disease • Neuroferritinopathy
	Structural lesions	• Stroke • Tumor

between 1 and 2% of musicians (15, 16). The hand that performs the more complex motor task appears to be preferentially affected (e.g., right hand in pianists, left hand in violinists, right hand in guitarists) (13). Musician's dystonia can be encountered with essentially all musical instruments, but certain instruments are overrepresented in clinical series of musician's dystonia, such as keyboard, guitar, and violin. The age at initiation of musical instruction appears to influence risk for development of the disorder, with instruction before age 10 being protective against the development of dystonia.

Typically musician's dystonia of the hand and arm begins as an insidious deterioration in previously automatic performance, followed by involuntary posturing within months of symptom onset (17). Dystonia may affect the fingers, wrist, upper arm, and even the shoulder girdle. Frequently, the pattern of dystonia segregates with certain instruments, for example adjacent finger flexion in pianists, wrist flexion in percussionists, and shoulder girdle involvement in the bow arm of violinists.

Current Knowledge Gaps and Areas of Controversy in Upper Limb Dystonia

The epidemiological studies of upper limb dystonia are widely believed to underestimate true prevalence rates, because many cases go unrecognized for many years or they are misdiagnosed as more common conditions, such as repetitive injury syndromes, Parkinson's disease, or tremor. One of the most common forms of task-specific dystonia is dystonic writer's cramp, but the prevalence of this form of focal dystonia has not been studied. In fact, one study revealed an average latency of more than 10 years from symptom onset to diagnosis for upper limb dystonias (18). Furthermore, agreement on diagnosis for upper limb dystonias is modest, even among experts (19, 20). The lack of widely accepted diagnostic criteria and reliable biomarkers for upper limb dystonias likely contribute to the poor diagnostic recognition and agreement.

Although there are multiple reports describing the clinical features for relatively large numbers of patients with cervical dystonia and craniofacial dystonia, few address upper limb dystonias. Most reports have included only relatively small numbers of patients with upper limb dystonia or they have focused on specific subtypes, such as writer's cramp (21–24), musician's dystonias (see below), or the dystonia associated with Parkinson-related neurodegenerative diseases (25–28).

The cause of musician's dystonia is obscure, but certainly seems multifactorial with different factors more important in different persons. The settings in which it most often develops involve repetitive performance of a movement that requires great skill. This setting implies the disorder is acquired due to certain environmental factors. While there are some genetic studies that have linked musician's dystonia in the arm and writer's cramp with variants in the arylsulfatase G gene, it remains unclear how genetics, environmental influences, and their interactions result in the development of the disorder (29). Classically considered to be an irreversible phenomenon, recent work has raised the possibility that early identification of patients and prompt initiation of treatment might rescue some patients, allowing them to continue their performing careers (30).

Although it is often claimed that 10–15% of patients with idiopathic Parkinson's disease may present with focal dystonia of the upper or lower limb, especially in early-onset cases, surprisingly few studies report the prevalence of this phenomenon, or of the clinical characteristics, that help to distinguish these cases from non-degenerative adult-onset focal limb dystonia (31, 32). The paucity of large clinical studies comparing the clinical features distinguishing the limb dystonias of degenerative Parkinson-related disorders from the limb dystonias of non-degenerative adult-onset isolated focal dystonias likely contributes to frequent misdiagnoses. Indeed, multiple studies have described patients with isolated limb dystonia who were misdiagnosed as having Parkinson's disease (33–36).

Some patients exhibit semi-rhythmical movements of the hand and arm, with little or no postural abnormality. When these movements occur only with writing, they are often called primary writing tremor. It remains controversial whether these types of abnormal movements should be classified as a subtype of dystonia (e.g., dystonic tremor), as a subtype of essential tremor, or as a distinct entity (37–44). Without a reliable biomarker for either dystonia or essential tremor, the exact classification will remain a matter of debate.

Dystonia of the Lower Limb

Focal or segmental dystonia confined to the lower limb is an uncommon focal dystonia and requires a meticulous assessment and testing to exclude other conditions, such as parkinsonism, stiff-person syndrome, and other movement disorders (45, 46). Runner's dystonia (RD), an important but often undiagnosed or misdiagnosed type of lower limb dystonia, is defined as a task-specific focal or segmental dystonia of the lower limb or trunk triggered by running (47). Patients with RD often describe their

initial symptom as a subtle change in their gait or running stride, a limp or a sense of pulling, cramping, or stiffness triggered by running and improved with rest. At first, they often attribute their symptoms to overuse, a change in shoes or a different running surface. They may also suspect "foot drop," an injury (muscle strain/sprain), or other musculoskeletal complaint (48). Commonly reported symptoms in RD include a limp when running, dragging of the foot or leg, inversion of the foot, scuffing of the toe, clipping an ankle with the opposite foot, trunk tilt, and/or pain. Similar to other focal dystonias, patients with RD may report an alleviating maneuver (also referred to as "geste antagoniste" or "sensory trick"), which improves their symptoms (49, 50).

When symptoms persist or worsen, a patient commonly self-refers to an athletic trainer/coach, physical therapist, sports medicine, or orthopedic physician—delaying the correct diagnosis often by many months or even by years (51). A missed diagnosis may also lead to unnecessary therapies and/or invasive procedures (52). By the time a patient with RD consults with a movement disorder specialist, their symptoms have often generalized to involve walking, and running may be limited or impossible. A possible clinical clue to the diagnosis of RD is a marked improvement in, or complete absence of, symptoms when the patient walks or runs backwards (i.e., task specificity).

Assessment of patients with suspected RD includes a history and physical examination with special attention to the musculoskeletal and neurological systems. The differential diagnosis of RD includes a focal dystonia presenting as the initial symptom of primary generalized dystonia, a secondary process (stroke, Parkinson's disease), trauma, and functional (psychogenic) causes (45, 53, 54). If not previously performed, the diagnostic work up may include electrodiagnostic testing, spine/brain/skeletal imaging, and laboratory studies including metabolic and, potentially, genetic testing. Functional assessment in RD includes observational and videotaped assessment of the patient at rest, standing, walking, and running. Video assessment may reveal subtle findings that are missed during real-time observation and can be used to evaluate the response to an intervention.

When RD is suspected and questions remain about the diagnosis after history and clinical exam, 3D computerized motion analysis may provide useful information about which muscles are involved. This method may help identify specific causes for this difficulty and guide treatments (55). Careful analysis of the electromyography (EMG) data is required paying special attention to the timing and duration of muscle activation, the relationship to kinematics, and side-to-side comparison. Abnormalities of muscle activation in patients with dystonia include onset, timing, duration, magnitude of recruitment, depression or prolongation of phasic bursts, and co-contraction; however, no studies have proven these tests to be diagnostic. Other abnormalities considered to be consistent with dystonia include activity at rest, an inability to relax when a movement ends, and overflow to an unwanted body part.

Current Knowledge Gaps and Areas of Controversy in Lower Limb Dystonia

Lower limb dystonia is less common than other focal dystonias, such as cranial and cervical dystonias, but its true prevalence is not known and is likely currently underestimated. Clinical features such as task specificity and the use of sensory tricks can be seen in lower limb dystonia, similar to other forms of dystonia. The relationship between isolated leg dystonia and other neurodegenerative diseases (i.e., Parkinson's disease) is not well understood.

Key Research Priorities in Clinical Features of Upper and Lower Limb Dystonias

- Development of clinical diagnostic criteria for upper and lower limb dystonias, taking into consideration their clinical heterogeneity
- Clarify the relationship between dystonia, tremor, and dystonic tremor
- Clarify the relationship between dystonia and mirror dystonia
- Systematic characterization of clinical characteristics of patients presenting with isolated limb dystonia who are likely to progress to Parkinson's disease or a related degenerative parkinsonian condition
- Characterize the genetic and environmental influences on the development of musician's dystonia

Posttraumatic Dystonia, Peripherally Induced Dystonia, and Complex Regional Pain Syndrome (CRPS)

Central (brain) trauma has been long recognized as a cause of dystonia, but peripherally induced dystonia, triggered by trauma to the cranial or peripheral nerves or roots, is still controversial (56). In a review of 190 articles presenting findings on 596 patients with peripherally induced movement disorders, the most frequently reported movement disorder was dystonia (74%), followed by tremor (23%), myoclonus (15%), spasms (11%), painful limbs moving extremities (6%); and another 2% had parkinsonism, chorea, and tics (57). Most studies reported latencies of less than 1 year (median = 21 days), but in 27 cases (5%) the reported interval between injury and the onset of movement disorder was greater than 1 year. Only 170 patients (29%) showed evidence of a nerve injury. Pain was an important feature in the majority of patients (81%) and preceded the onset of movement disorder in 20% of the cases. CRPS was diagnosed in 42% of the reported cases but only 8% had nerve injury. BoNT was the most frequently applied therapy (21%) in this review, with 57% of patients treated with BoNT reporting mild or moderate improvement in symptoms. Physical therapy and oral medications, such as trihexyphenidyl, baclofen, and muscle relaxants, provide only limited benefit in this population. Due to a concern of abnormal sympathetic drive in this disorder, chemical and surgical sympathectomies have been used in this patient population, but due to common complications after sympathectomy and lack of evidence of clear long-term benefit, it is now rarely used (58). Deep brain stimulation (DBS) has been only rarely reported to be beneficial in patients with peripherally induced dystonia (59).

Despite strict diagnostic criteria, including the requirement for anatomically and temporally related injury, the cause-and-effect relationship between the peripherally induced injury and subsequent movement disorder may not be obvious in all cases.

Although the pathophysiological mechanisms of peripherally induced movement disorders are not well understood, emerging evidence suggests that individual (e.g., genetic) predisposition, coupled with central reorganization in response to the altered peripheral input, plays an important role in the pathogenesis of peripherally induced movement disorders (**Figure 1**). Arm immobilization, a form of peripheral injury, can lead to decreased thickness in the contralateral primary motor and somatosensory cortical area and a decrease in the white matter fractional anisotropy in the contralateral corticospinal tract (60). Cortical reorganization in the primary sensorimotor cortex occurs following arm amputation (61). Abnormal activation on functional magnetic resonance imaging (fMRI) in regions such as the basal ganglia and other brain regions reported in patients with CRPS have not been confirmed by other studies (62). This may be partly explained by heterogeneous population of patients, small sample size, and methodological issues related to fMRI (63).

Current Knowledge Gaps and Areas of Controversy in Peripherally Induced Dystonia

One of the major sources of debate related to peripherally induced dystonia is its possible relationship to functional (psychogenic) movement disorders. This controversy is particularly highlighted by the phenomenon of "fixed dystonia." In the classic report by Schrag et al., the authors described the clinical features of 103 patients presenting with fixed dystonia, primarily (90%) involving the limb (64). They followed 41 patients prospectively for a mean of 3.3 years. In 63% of patients, the dystonia was preceded by a peripheral injury and in 56% the dystonia spread to other body regions. During the follow-up period, only 27% achieved partial or complete remission. Pain was a major complaint in 41% of the patients, and 20% met the criteria for CRPS. Although only 37% of the patients fulfilled diagnostic criteria for "documented or clinically established psychogenic dystonia," the authors concluded that "many patients fulfill strict criteria for a somatoform disorder/psychogenic dystonia" and that fixed dystonia "usually, but not always, occurs after a peripheral injury and overlaps with CRPS" (64). Other studies have failed to establish direct connection between CRPS and an abnormal psychological profile (65). Many patients with CRPS, however, share demographic and clinical features with those diagnosed as functional (psychogenic) movement disorders, such as female preponderance, young age, and abrupt onset (64). Although no specific abnormalities in brain structure or function have been consistently identified in patients with CRPS, it would be premature to conclude that CRPS is a functional (psychogenic) disorder (62).

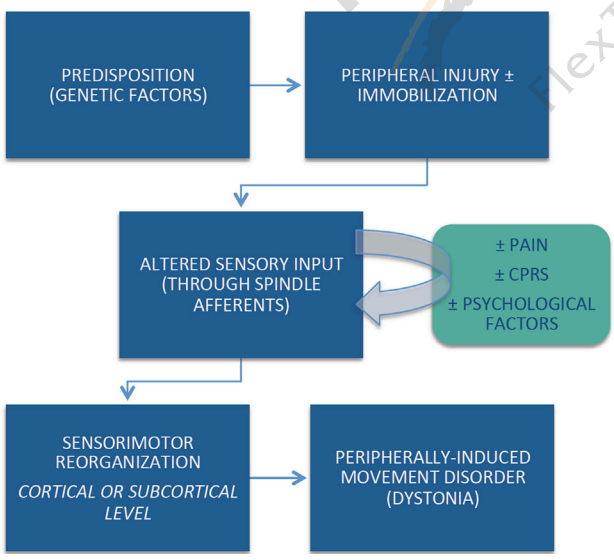

FIGURE 1 | Diagram of hypothesis of peripherally induced movement disorders.

In addition, there are other controversies concerning the diagnosis and the pathophysiology of peripherally induced or posttraumatic dystonia. Besides peripheral injury, prolonged immobilization seems to be an important risk factor. One distinguishing clinical feature from other dystonias is the frequency of pain as a presenting complaint. Although local injections of BoNT into the muscle of the dystonic limb or an intradermal injection in the region of the pain may improve the motor and sensory aspects of CRPS-related dystonia, therapeutic options for this disorder currently are limited and have not been systematically studied to date (66).

Key Research Priorities in Peripherally Induced Dystonia

- Systematic clinical and neurophysiological characterization of patients with peripherally induced dystonia compared to focal, idiopathic limb dystonia, and to healthy controls
- Investigation of patients with pre-existing dystonia following peripheral injury and/or immobilization using epidemiologic, phenomenologic, neurophysiologic, and imaging studies to identify any factors that might exacerbate underlying dystonia to provide insights to peripherally induced dystonia
- Development of a suitable animal model that can explore the effects of peripheral injury on spinal cord and brain and its role in centrally mediated dystonic symptoms
- Design and conduct double-blind, controlled clinical trials of BoNT in patients with peripherally induced dystonia to establish the level of evidence that this treatment modality is safe and effective in this population

PATHOGENESIS

Inhibition in Dystonia: Motor and Sensory

The pathophysiology of dystonia is characterized by a loss of inhibition, which has been shown at multiple levels in the nervous system, from the spinal cord to the brainstem to the motor and sensory cortical regions (67). This loss of inhibition manifests in the periphery with abnormally long muscle bursts as measured by EMG, co-contraction of agonist and antagonist muscles, and overflow into adjacent muscles not needed for the particular motor task (67).

Several measures of cortical excitability examined in focal limb dystonia have revealed abnormalities including short intracortical inhibition, mediated through GABA-A receptors, and long intracortical inhibition, mediated by GABA-B (68). Another measure of cortical excitability is the cortical silent period (CSP). The CSP is a pause occurring during voluntary movement after a pulse of transcranial magnetic stimulation (TMS) is applied to the contralateral motor cortex. There are both spinal cord and cortical inhibitory contributors to the CSP, the latter likely mediated through GABA-B receptors (69, 70). In writer's cramp, the CSP is shortened compared to controls, indicating an overall loss of inhibition in the motor system (71). Interestingly, this finding has been seen only in the symptomatic hand and not in the asymptomatic side. Further specificity was seen in a study of writer's cramp where the CSP was significantly shorter in the patient group only during a pincer grasp but not during a power grip condition, suggesting some task specificity in this abnormality (72). During a pilot trial examining individualization of therapeutic repetitive TMS in two focal hand dystonia patients, one of the response variables used was the CSP (73). The investigators found that the subject with the shortened CSP responded favorably to the repetitive TMS (rTMS) and had both a physiological response with lengthened CSP and a subjective clinical improvement (73).

While as noted above, the pathophysiology of focal dystonia has generally shown a loss of inhibition, there are some examples in the literature of enhanced inhibition in dystonia patients in particular cortical pathways. A dorsal premotor to primary motor cortex abnormality has been identified in writer's cramp patients at rest, where the writer's cramp show enhanced inhibition compared to healthy controls (74). This inhibitory influence from the premotor cortex (PMC) was found to be supraspinal in nature, as the H-reflex did not change with premotor conditioning. Evaluating this abnormal premotor–motor interaction through a biomarker analysis showed an area under the curve of 0.825 with a sensitivity of 84% and specificity of 74% (74). Whether this abnormality is a primary manifestation of the disease or is a compensatory change is not clear, but a pilot trial enhancing inhibition over the PMC in cervical dystonia has shown some promise (75).

Abnormalities in inhibition in the sensory system have also been identified in focal dystonia—specifically in the somatosensory temporal discrimination threshold (STDT). The STDT is the shortest time interval necessary for a pair of tactile stimuli to be perceived as two (76). STDT has been shown to be abnormal in dystonia, including focal hand dystonia (77, 78) and in cervical dystonia (79). However, abnormalities in STDT are not specific for dystonia as they may be seen in other patient populations (e.g., Parkinson's disease) (80). The pathophysiology of abnormal STDT has been demonstrated to be due to a loss of a short latency inhibitory process (78). Using inhibitory non-invasive neurostimulation, the STDT was increased in healthy volunteers (81). This led to the clinical effect of overall decreased ability to discriminate between paired inputs, suggestive of at least *part* of the phenotype seen in dystonia. This may be an instructive tool to improve our interpretation of abnormal STDT and recapitulate part of the phenotype in a human "model."

Plasticity in Dystonia

Another theme that has emerged in the pathophysiology of focal dystonia is aberrant cortical plasticity. One widely used method to assess cortical sensorimotor plasticity is paired associative stimulation (PAS). Repeated pairs of peripheral nerve stimulation, typically median nerve stimulation at the wrist, followed by TMS of the motor cortex (M1) between 21 and 25 ms later, induce cortical plasticity. This produces a spike-timing dependent, long-term potentiation (LTP)-like plasticity at the level of the M1, also known as associative plasticity. Initial studies in patients with writer's cramp showed excessive plasticity with abnormal spread of the induced plasticity to non-targeted muscles (82, 83). The increased LTP-like plasticity extends to body parts unaffected by dystonia. For example, patients with cervical dystonia, blepharospasm, and oromandibular dystonia, all had excessive plasticity measured in their unaffected hand muscles (84).

The ability to regulate plasticity to keep excitability within a useable range, known as homeostatic plasticity, is also impaired in dystonia (85). In addition to examining motor cortical plasticity, studies have also measured somatosensory-evoked potentials and found increased LTP-like plasticity in the somatosensory cortex in patients with focal hand dystonia (86). Taken together, these studies lead to the attractive hypothesis that task-specific hand dystonia is related to excessive plasticity, possibly due to abnormal association between sensory input and motor output with deficient homeostatic control (87).

It should be noted, however, that several studies did not find increased sensorimotor plasticity in focal hand dystonia using PAS, and the results from different studies have varied (88). Some of these conflicting results may be due to the inherent variability of the effects of PAS even in healthy subjects (89, 90). In addition, there is also variability in the PAS paradigms resulting in differing times between median nerve stimulation and TMS (e.g., 21.5 vs. 25 ms) (91). Other factors including the repetition rate, the stimulus strength and the number of paired stimuli delivered, the state of muscle activity, the time of the day, attention to the stimuli, and genetic factors, all are important factors in measurements of plasticity (92). Another form of LTP-like cortical plasticity induced by intermittent theta burst stimulation, which does not involve sensory input, showed abnormal plasticity but was *decreased* rather than increased in focal hand dystonia (93). These findings suggest that abnormal processing of sensory input may underlie increased associative plasticity in focal hand dystonia, but the direction of change is variable depending on the study paradigm and the exact part of the sensorimotor cortex probed.

One way to understand the role of plasticity in dystonia is through the relationship between associative plasticity and the effects of DBS, a therapy used to treat generalized dystonia and less often, focal dystonia. DBS targeting the globus pallidus interna (GPi) decreases excessive associative plasticity in patients with generalized dystonia (94). However, the time of the maximum decrease in plasticity occurred before the subsequent, maximum clinical improvement, raising the possibility that the reduction in excessive plasticity may drive clinical improvement (94). Moreover, in patients with generalized dystonia who had the DYT1 gene mutation, the degree of associative plasticity correlated with the maintenance of clinical benefit after GPi DBS was turned off

for 2 days (95). In these patients, associative plasticity seemed to reflect an ability to store normal movements and to resist abnormal signals from the basal ganglia even while the therapy was turned off. Direct measurement of GPi activity during DBS implantation has also provided evidence that short-term plasticity is abnormal in dystonia patients, with impaired paired-pulse depression seen (96). This and other studies suggest that the impaired inhibition seen cortically in associative plasticity studies is also reflected at the basal ganglia level in direct recordings (96–98).

Task Specificity

One of the most fascinating features of limb dystonia is task specificity. This refers to the situation where dystonia is manifested only during a single task or several closely related tasks, such as in writer's cramp and in musician's dystonia (e.g., pianist's cramp is only manifested when playing the piano). Although more common in the upper limbs, task-specific dystonia can also affect the face (e.g., embouchure dystonia) and the leg (e.g., RD). As discussed earlier, the dystonia appears to be triggered, at least in part, by repetitive skilled action, and virtually any task can be affected. At onset, the dystonia can be very highly selective; some cases of writer's cramp, for example, have begun with involvement of only a few specific letters. Moreover, the dystonic posture can be highly focal involving only one or two fingers. While many patients with a task-specific dystonia remain with relatively restricted involvement, the dystonia can spread to involve more muscles, becoming segmental dystonia or even more generalized dystonia. In some patients, the task specificity is gradually lost with dystonia affecting more tasks or even appearing at rest.

Why does repetitive activity drive the development of a task-specific dystonia? Much evidence suggests that repetition, in-and-of-itself, is not the sole driver, but that it is the interaction of repetitive activity with multiple factors. One likely factor is a genetic predisposition. Another is inherent biomechanical abnormality of the hand (99). If the hand is anatomically abnormal, then the motor control program might require modification in order to accomplish the intended motor task. Another critical factor seems to be abnormal plasticity processes in the brain. As noted above, good evidence suggests that patients with limb dystonia have abnormal homeostatic mechanisms to control the upper and lower bounds of plasticity as well as heightened plasticity overall, which is widespread both anatomically as well as within the different dystonia types (100). The abnormalities of plasticity suggest an endophenotype, not necessarily the cause of dystonia by itself, but predisposing to the development of dystonia. The combination of repetitive activity, heightened plasticity, and failure of limiting plastic change may well be the particular combination needed to drive the development of dystonia.

How is it possible to have a task-specific deficit? Considering writer's cramp, for example, motor control in the hand itself is basically working since all actions except writing are done well. Moreover, the motor program for writing remains intact since writing can be done normally with other limbs, albeit somewhat clumsily. Hence, task specificity arises just with the particular conjunction of a specific limb with a specific task. The pattern of brain activation with a specific body part is well established with somatotopic involvement of the primary motor cortex, cerebellum, and lateral and medial PMC. The motor program for writing has also been studied and includes parts of the PMC and parietal areas. A special area in the PMC concerned with writing is Exner's area—near and analogous to Broca's area for speech. A specific subset of the overlap between these two regions must be responsible for writing with the dominant hand, the usual limb for writing and, therefore, the body part at risk for the development of dystonia. In an fMRI experiment to determine task-specific activation, stronger activations in the left dorsal prefrontal cortex, left intraparietal sulcus, and right cerebellum in writing were found compared with all other tasks. Additionally, the left anterior putamen was active at onset for all the tasks, but only showed sustained activation during the right-hand writing. An exploratory analysis showed clusters in the left ventral PMC and inferior and superior parietal cortices that were only significantly active for right-handed writing (101).

A similar experiment was conducted in patients with writer's cramp. The regions that were task-specific in the normal individuals were less active in patients. Moreover, the connectivity between the parietal and premotor areas was less strong (102). Hence, it appears that a specific parietal–premotor pathway was malfunctioning. In some sense, this is not surprising. Individual parietal–premotor pathways do seem specialized for specific tasks. This has been demonstrated most clearly for a reach-to-grasp movement, where there are separate pathways for each component (103). Moreover, large lesions of either parietal or premotor areas will cause apraxia with a loss of many skilled movements (104). Thus, a task-specific deficit could arise from the interaction of a pathway where a specific task was learned together with excessive motor repetition of that particular task in the setting of uncontrolled plasticity.

Functional Imaging of Limb Dystonia

Functional imaging in isolated limb dystonia has helped to identify underlying pathophysiologic mechanisms, as exemplified in the previous section. Various functional neuroimaging methods have been used with other goals in mind and include molecular imaging focusing primarily on brain hemodynamics or changes in dopaminergic pathways and fMRI of resting-state blood oxygen level dependent signals.

Positron emission tomography (PET) measures of regional cerebral blood flow can identify local blood flow responses to various stimuli. The general strategy has been to measure blood flow with the participant at rest in the scanner and then repeat the PET measure during an activation procedure. Local changes in either blood flow or metabolism reflect local neuronal activity or the changes in activity of terminal fields projecting to that area (105). Initial studies of brain responses to hand movements in people with isolated upper limb dystonia revealed differences in blood flow responses. However, differences in how someone with hand dystonia and a control subject move the hand could substantially confound interpretation of such studies. This methodologic ambiguity and the observation of sensorimotor integration problems in people with hand dystonia led to studies of blood flow responses to sensory driven stimuli.

Vibration of a hand produces a blood flow response in contralateral sensorimotor cortex and supplementary motor area.

People with isolated hand dystonia, including a subgroup with only right-handed writer's cramp, show an approximately 25% reduction in these blood flow responses (106, 107) similar to findings in other isolated dystonias (108). The vibratory stimulus elicited a cramp in some of the dystonic participants, but these participants did not have a different blood flow response from those who did not have cramping. The healthy controls who simulated a dystonic posture during the vibratory stimulus had an increased, rather than decreased blood flow response. Similarly, a patient with dopa-responsive dystonia showed reduced blood flow response to vibration that normalized after a dose of L-DOPA (109). This observation suggested that the vibration-induced blood flow responses could be influenced by dopaminergic pathways.

Positron emission tomography also can provide direct measures of dopaminergic receptors with most studies finding a reduction in D2-like dopaminergic receptors. MPTP, a neurotoxin selective for dopaminergic neurons, when given *via* one internal carotid artery in non-human primates, produces contralateral transient limb dystonia followed by chronic parkinsonism (110, 111). During the transient dystonic phase, striatal D2-like receptor binding is reduced about 25–30% but then increased several fold during early parkinsonism. The increased D2-like receptor binding gradually returned toward normal. However, mRNA selective for D2R (selective for D2R over D3R) revealed no change whereas mRNA for D3R did increase coinciding with the D2-like receptor changes (112). These findings presaged studies in humans with isolated limb dystonia that revealed a similar reduction in striatal D2-like binding in those with either isolated, idiopathic hand, or cranial dystonia (113–115). In fact, the site of change in the putamen seems to relate somotopically to the part of the body involved (116). Some have used [^{11}C] raclopride as the D2-like radioligand. This particular radioligand can be displaced by increased release of endogenous dopamine. This characteristic has permitted measures of striatal dopamine release in response to drugs or tasks. In particular, a finger-tapping task elicited less dopamine release (measured as a change in striatal uptake of [^{11}C]raclopride) in people with writer's cramp whereas a speech task in those same subjects yielded greater striatal dopamine release (115). Key findings from these studies is that striatal D2-like receptor binding is likely abnormal in limb dystonia and changes in dopamine release may also occur.

The selectivity of these changes for specific D2-like dopamine receptors remains unclear. PET measures with a D2 highly selective radioligand [^{18}F]*N*-methyl benperidol (D2 ≫ D3 selectivity) did not reveal any changes in people with either hand or cranial dystonia (117). This suggests that the findings with less selective D2-like radioligands may reflect a change in D3 dopamine receptors, which would be consistent with the observation in MPTP-induced transient dystonia in monkeys (110–112); however, confirmation of this notion awaits development of a highly selective D3 radioligand for PET. Nevertheless, D1-like dopamine receptors appear to be normal in hand and cranial dystonia (118). Thus, these studies indicate a change in dopamine receptors possibly due to a change in striatal D3 specific dopamine receptors in dystonia patients.

At this point, the focus has been on neuroimaging findings that relate to changes in striatal function or activity. Yet, increasing data suggest that the dystonia also may reflect changes in cerebellar function that may result from either direct involvement of cerebellum by functional connections with other brain regions or networks. Resting-state functional connectivity studies with magnetic resonance imaging (rs fcMR) have demonstrated strong functional connectivity in humans between striatum and a large area extending from upper and middle brainstem into cerebellum (119). These findings do not necessarily reflect direct anatomic connections but evidence for direct connections in non-human primates between the cerebellum and the subthalamic nucleus *via* the pons (120). The cerebellar vermis also has direct connections to primary motor and premotor areas (121)—areas that also have functional connectivity with the striatum. Thus, dysfunction in a brain network, either precipitated by direct involvement of a specific node or modulation at the network level, may provide the underlying pathophysiology of limb dystonia.

In support of this notion, rs fcMR studies indicate reduced functional connectivity between inferior parietal lobule and dorsal PMC contralateral to right-handed writer's cramp patients (122). Another rs fcMR studied revealed increased functional connectivity with the left putamen as a component of the default mode network (DMN) in 16 people with right hand writer's cramp compared to controls. Although the putamen is not typically considered part of the DMN, a network that includes prefrontal, anterior and posterior cingulate, lateral parietal, inferior and middle temporal area, cerebellar areas, and thalamus (123), the comparison of the independent component containing the DMN between the writer's cramp and control groups revealed this increased putamen functional connectivity (124). In this same study, the writer's cramp group had reduced functional connectivity with the left PMC that was part of the sensorimotor network. Both of these findings were affected by BoNT injections. The advantage of these resting-state studies is that they are not confounded by either behavioral changes during the scanning sessions or performance differences that could differ between those with limb dystonia and control groups.

Current Knowledge Gaps and Areas of Controversy in Dystonia Pathogenesis

The pathophysiology of focal limb and task-specific dystonia is characterized by a loss of inhibition, impaired sensorimotor integration, and aberrant cortical plasticity as seen through non-invasive neurostimulation studies. How precisely task specificity emerges from these underlying neurophysiologic changes is not known; but, factors such as an underlying endophenotypic trait of abnormal plasticity combined with repetitive task-specific movement generated in a particular sensorimotor network—all appear relevant. This issue is a key area to focus on moving forward in order to clarify how plasticity abnormalities translate into the clinical expression of dystonia. In addition, functional neuroimaging studies have revealed changes in dopaminergic pathways in the striatum and altered striatal and cerebellar pathways in dystonia patients. Together, these various findings suggest that changes at the network level underlie limb dystonia and raise questions about whether cortical–striatal–thalamo cortical networks are really segregated from cerebellar–thalamic–cortical networks. In particular, the relationship with the dopaminergic

system in dystonia is intriguing and worthy of future exploration. This includes further invasive and non-invasive paired-pulse studies (such as in GPi DBS for dystonia). As mentioned earlier, the relationship between isolated focal limb dystonia and post-traumatic, peripherally induced dystonia is unclear. There have been several studies aiming to explore at this question. A recent study looking at patients with a fixed hand posture and CRPS compared to healthy controls found sensorimotor abnormalities potentially compatible with a psychogenic dystonia and in contrast to findings found in isolated focal hand dystonia (125). Identifying similarities and contrasts between the underlying pathophysiology of these disorders will be helpful moving forward perhaps both in diagnosis and in treatment.

Key Research Priorities in Limb and Task-Specific Dystonia Pathogenesis

- Further studies to distinguish cause from effect in both physiology and imaging studies, so that attention can be directed to the most relevant biological correlates of dystonia
- Development of a diagnostic battery using neurophysiologic and imaging tests, including identifying whether one test will be sufficient for all focal dystonias
- Identification of therapeutic targets
- Understand the variability and reproducibility of PAS and other non-invasive measurement tools in healthy subjects and dystonia patients and standardization of study protocols to minimize variability across studies
- Determine how exactly abnormal plasticity affects the specific parietal–premotor pathway and how this relates to spread of dystonia beyond a particular task or limb

THERAPY

BoNT for Treatment of Limb and Task-Specific Dystonias

Botulinum toxin has a well-recognized role in the treatment of limb and task-specific dystonias; although, the amount of Level I evidence available is limited (126). Currently, three BoNT type A formulations (onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA) are approved for upper limb spasticity and only one, onabotulinumtoxinA, for lower limb spasticity (127). None of these are approved, however, specifically for focal limb dystonia.

Several randomized, double-blind, controlled studies in limb dystonia have been performed investigating abobotulinumtoxinA (128, 129) and onabotulinumtoxinA (130–132). When comparing these studies, outcome measures and populations enrolled have marked variability. This highlights one characteristic of focal limb dystonia that makes obtaining reliable data on efficacy challenging. Standardized scales or outcome measures capturing all types of task-specific or limb dystonia are lacking. In addition, the very nature of task specificity makes it difficult to generalize, and its clinical manifestation and prevalence tend to change with occupational skills relevant to the era and to the particular society (133). The impact on quality of life is very patient-dependent, and treatment response is at times radically different from other conditions responsive to BoNT therapy (134). Another area of interest is the choice of toxin for specific indications. To date, no Level I studies have been performed allowing a comparison of available formulations for limb and task-specific dystonia. Comparative studies have been conducted in blepharospasm and cervical dystonia populations, but it is not clear to what extent the results can be extrapolated to focal limb dystonia.

Regarding injection technique, accurate targeting of the relevant muscles, and avoidance of toxin spread to adjacent structures are clearly desirable. Little data are available, however, on the best guidance tools among the available options. There is some evidence that using a guidance method, such as EMG, is superior in accuracy to anatomic guidance alone (135) but it is not clear how this translates into efficacy. This issue of efficacy has been studied in limb spasticity, comparing electrical stimulation and ultrasound guidance (136, 137) but not in limb dystonia. Studies are ongoing comparing guidance techniques in this patient population (Clinical Trials identifiers NCT02334683; NCT02326818), and more are needed.

Rehabilitation Interventions for Limb Dystonias

Given the sparse literature on the topic and the rarity of the disorder, there are no clinical practice guidelines on rehabilitation in upper or lower limb dystonia. However, conventional rehabilitation methods, such as stretching, strengthening exercises, manual therapy, and splinting programs, are frequently used in clinical settings when patients are referred for physical or occupational therapy. These therapies are also often tested as a control intervention or combined with other therapies in research investigating efficacy of a novel intervention protocol (138–140).

In limb dystonia patient populations, investigators have proposed various forms of intensive motor training to recover voluntary motor control. These approaches have been frequently explored in treatments of musician's dystonia using the methods known as "slow down therapy" and "sensorimotor retraining" (141). Other approaches have prioritized the reorganization of the cortical somatosensory map using methods, such as Braille training (142, 143), "learning-based sensorimotor training" (138, 139, 144), or prolonged immobilization of the affected limb (this method is no longer used) (145, 146). Attempts to normalize muscle activity to restore voluntary control using biofeedback, vibration, or electrical stimulation have also been used (147–151). Similar to constraint-movement therapy, a method often used in stroke rehabilitation, some investigators have used motor practice combined with constraining the unaffected joints with the goal of decreasing compensatory movements (152, 153). Finally, combining neuromodulation methods with motor training in an attempt to normalize brain excitability and further improve motor performance has been tried either with transcranial direct current stimulation (tDCS) (154–156) or with rTMS (140).

Despite the different theoretical bases of the interventions, when considered together, rehabilitation studies in limb dystonia suggest positive outcomes (157–159). Significant improvements have been reported in rating scales of dystonia severity, arm disability, quality of musical performance, and quality of life (140, 144, 153, 160, 161). Studies that focused on sensory reorganization have

reported increase in sensory discrimination (138, 139, 142, 144). Furthermore, improved motor performance in writing, gait, and musical performance has also been reported (142, 153, 161, 162).

Limitations of the above studies are typical of small-scale trials and include lack of control groups, blinding, or randomization. It is also likely that the interventions tested were of insufficient duration, considering that limb dystonia likely develops over a long period of time. As the rehabilitation research in limb dystonia develops, it will be important to investigate comparative effectiveness of interventions to understand which approach holds the most promise and the neurophysiological mechanism of effect. Given the nascent stage of rehabilitation research in focal dystonias, full-scale clinical trials have yet to be conducted. Thus, definitive statements cannot yet be made regarding efficacy and clinical implementation of a particular methodology.

A major challenge of rehabilitation intervention studies in general is determining an appropriate control and clearly specifying the interventions to improve reproducibility. The hallmark of rehabilitation is that it involves active participation by the patient and is tailored to each patient's unique need, which can create problems for reproducibility. For a control to be effective, it must be believable as a true intervention but not contain the key components of the experimental condition. Indeed, blinding and control are essential for future studies, as care from a therapist may impart benefits secondary to feeling cared for in addition to a pure placebo effect. Consequently, future investigations in dystonia need to carefully address this issue by comparing different treatment strategies with similar frequency, duration, and interaction between patient and therapist.

Study designs in a rare and heterogeneous disorder, such as dystonia, require careful consideration outside of the gold standard multisite, randomized controlled trial. Small-scale trials are appropriate given our limited understanding. However, studies should utilize robust small *n* methodology such as single subject experimental design studies with repeated measures (163).

Non-invasive Brain Stimulation and Hand Dystonia

Non-invasive brain stimulation techniques, such as rTMS and tDCS, have been applied in both basic research into the pathophysiology of hand dystonia and in therapeutic trials (164). Both methods can alter brain excitability in sensorimotor networks, which can be used to reduce abnormal excitation in sensorimotor cortex. The precise neurophysiological mechanisms underlying this change in excitability are not fully understood; however, high frequency rTMS and anodal tDCS are able to increase excitability of the sensorimotor cortex (165). Low-frequency rTMS and cathodal tDCS achieve excitability changes in an inhibitory direction (165). The effects of non-invasive neurostimulation are far more complex than unidirectional excitability change and are not limited to the site of the stimulating electrodes but extend to frontal and parietal networks as well as to the basal ganglia and to the cerebellum (166, 167).

Several small controlled therapeutic trials of writer's cramp have been done with inhibitory low-frequency rTMS (164). Studies typically included less than 10 mostly writer's cramp subjects and most used a crossover design with a single session of stimulation targeting the contralateral hemisphere to the dystonic hand. Siebner et al. found that M1 stimulation modestly improved focal hand dystonia (168); however, Murase et al. showed that PMC was a better target than M1 and supplementary motor area to reduce writer's cramp symptoms (169). Subsequently, more studies used PMC as the target in multi session interventions and showed promising results either by physiologic or behavioral measures (170, 171). rTMS combined with sensorimotor retraining did not provide objective improvements in patients despite subjective improvement in six of nine (73). The results of these small-scale clinical trials with low-frequency rTMS have been mixed, and it is not currently ready for clinical application in this population.

In the last years, tDCS has gained popularity, partly due to its simple application combined with its low cost and low risk for adverse events. In patients with musician's dystonia (e.g., professional guitarists), a single session of cathodal tDCS targeting the affected M1 did not improve the performance of guitar playing (172). Similarly in pianists, a single session of cathodal or anodal tDCS of the affected M1 combined with simultaneous retraining consisting of slow, voluntarily controlled movements on the piano did not result in any improvement in dystonia (173). The same strategy did not help patients with writer's cramp (174). In contrast, cathodal tDCS of the affected M1 and simultaneous anodal tDCS of the unaffected M1 in dystonic pianists improved the rhythmic accuracy of sequential finger movements with the affected hand, but only if concurrent bimanual mirrored finger movements were performed (155). This improvement lasted for 4 days after the intervention. Neither a reversed montage of electrodes (anodal tDCS of the affected M1, cathodal tDCS of the unaffected M1) nor unilateral anodal tDCS of the unaffected M1 or sham stimulation yielded any improvement (155). Furthermore, the amount of motor improvement correlated directly with the severity of the symptoms, that is, the most severely affected patients benefited most from the intervention. These findings suggest therapeutic potential in behavioral training assisted by bihemispheric and polarity-specific tDCS in restoring fine motor control in musician's dystonia. A further single-case study showed augmented therapeutic effects through bihemispheric tDCS combined with bimanual mirrored retraining over two successive days (175). Another group explored biparietal tDCS during neurorehabilitation and showed improvement in dystonia severity in musicians (156).

DBS and Limb Dystonia

Deep brain stimulation targeting GPi is a highly effective treatment for medically refractory isolated generalized dystonia, supported by high quality case series and randomized controlled trials (176). Patients with cervical dystonia who respond neither to medications nor targeted injections of BoNT may also benefit from DBS, but less reliably so (177). In contrast, the experience treating focal limb dystonia with DBS is quite sparse, most likely because this form of dystonia is uncommon and rarely debilitating, so that the potential risks of DBS surgery seem unwarranted. On the other hand, task-specific dystonias may force an individual to forego an activity that makes his or her life meaningful and BoNT injections can yield significant weakness in both the treated and adjacent muscles, denying the individual the fine

motor skills required to perform the practiced task despite relief of their abnormal dystonic posture.

A review of the literature regarding stereotactic surgery for focal limb dystonias reveals the following: (1) fewer than 50 patients who have undergone a brain surgery for either writer's cramp or musician's dystonia are reported in the literature; (2) all of these patients were operated in either Korea or Japan; (3) the majority were treated with ventralis oralis thalamotomy, the rest with thalamic DBS; and (4) the results were uniformly positive, though assessed in an un-blinded fashion with relatively short follow-up (178–181). There is virtually no literature regarding the use of pallidal surgery (ablation or DBS) for focal limb dystonia.

Given these reported results, the fact that DBS is a safe intervention in skilled hands (incidence of serious neurologic injury: 1–2%), and the opportunity to address an unmet need with this targeted intervention, it would seem that a more rigorous evaluation of thalamic DBS for focal limb dystonia is appropriate. However, the small but real risk of catastrophic stroke/hemorrhage and the fact that focal limb dystonia is neither life-threatening nor always debilitating, mandate that these studies be conducted at comprehensive movement disorders centers that include both an experienced DBS surgeon with a documented low surgical complication rate and neurologists facile both in the treatment of focal limb dystonia and the programming of DBS devices.

Current Knowledge Gaps and Areas of Controversy in Therapy in Focal Limb Dystonia

Botulinum toxin therapy is often applied in an off-label manner in focal limb and task-specific dystonia but only limited evidence supports this practice due to the heterogeneity of the condition and to a lack of standardization in practice and data collection. Despite limitations, studies of rehabilitation in limb dystonias, as well as anecdotal reports, suggest a potential for improved outcomes for patients with rehabilitation intervention delivered by a therapist trained in the unique needs of a patient with dystonia, but definitive efficacy of a specific approach remains to be demonstrated. Non-invasive (rTMS and tDCS) and invasive (DBS) therapeutic modalities have been explored in only a small number of limb and task-specific dystonia patients and in studies with design limitations, which hampers the ability to move forward currently to larger clinical trials and to expand these potential therapies into clinical practice.

Key Research Priorities in Therapy in Focal Limb Dystonia

- BoNT: refine the role of BoNT therapy by optimizing practice, developing new formulations, and use of combination therapeutic modalities (such as BoNT combined with physical therapy or neuromodulation)
- Rehabilitation: determine appropriate controls, understand the neurophysiological effects of rehabilitation for limb dystonias, determine best frequency and duration for interventions given that a long period of time likely is required for symptom development, determine duration of benefits after rehabilitation interventions
- Non-invasive brain stimulation: future trials to take into consideration the dose and duration of stimulation protocol, predictive markers for responders, designs which allow between and within subject effects to be explored and combination with specific motor retraining procedures
- Invasive brain stimulation: design randomized controlled trials with good subject characterization
- Identifying the triggering movement, and differentiating primary vs. compensatory movements is critical for selection of the best muscles for BoNT injection in musician's dystonia
- Development of an effective therapeutic strategy including early identification of patients, prompt initiation of treatment as well as new and better therapies, and modification of the "every three months" BoNT injection paradigm to fit the schedule and needs of a performing artist

TABLE 2 | Themes in focal limb dystonia research priorities.

Diagnosis	Development of diagnostic criteria	• Upper limb • Lower limb • Peripherally induced
	Standardize neurophysiologic tests	• CMA • Paired associative stimulation (PAS)
	Development of diagnostic battery using neurophysiology and imaging tests	• Somatosensory temporal discrimination threshold • Functional magnetic resonance imaging
Phenotypic characterization	Isolated focal limb dystonia	• Relationship to neurodegenerative disease
	Peripherally induced dystonia	• Identify factors that are protective or promoting
	Tremor, dystonia, dystonic tremor	• Clarify the relationship of tremor with dystonia
	Genetic and environmental influences	• Isolated limb dystonia and task-specific dystonia
Pathophysiology	Loss of inhibition	• Understand how a loss at a network level translates to a focal symptom
	Abnormal plasticity	• Understand the variability in PAS response
	Task specificity	• Understand the relationship between repetition and abnormal plasticity
	Peripherally induced, posttraumatic	• Understand commonalities and differences between isolated dystonia and posttraumatic
Therapy	Clinical trial development	• Innovative designs with small *n* • Duration of therapy needed for a disease that took years (or decades) to develop • Harness the inter-patient variability • Standardize outcome measures
	Development of therapeutic targets for invasive and non-invasive neurostimulation	• Target localization for all focal limb dystonias • Systematic assessment of duration and stimulation parameters

SUMMARY

Focal limb dystonias, from the task-specific to the peripherally induced, share clinical features with the other focal dystonias such as the adult-onset nature of the disease and the presence of sensory tricks that can temporarily ameliorate dystonic symptoms. However, the focal limb dystonias have a clinical heterogeneity (e.g., pianists dystonia and RD), which makes design of studies complicated from choosing specific anatomical targets for therapeutic interventions to developing comprehensive outcome measures that can fully quantify change in symptoms given high variability at baseline (**Table 2**). Focus on the research priorities as outlined here aims both to advance diagnostic capabilities and knowledge of the pathophysiology of this disorder, but also, to develop innovative therapeutic strategies to keep focal limb dystonia patients writing, running and performing.

AUTHOR NOTES

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AUTHOR CONTRIBUTIONS

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Exploring factors related to physical activity in cervical dystonia

Abstract

Background: People with disabilities have reported worse health status than people without disabilities and receiving fewer preventive health services such as counseling around exercise habits. This is noteworthy considering the negative consequences associated with physical inactivity. No research has been conducted on physical activity in cervical dystonia (CD), despite its possible major impact on self-perceived health and disability. Considering the favorable consequences associated with physical activity it is important to know how to promote physical activity behavior in CD. Knowledge of variables important for such behavior in CD is therefore crucial. The aim of this study was to explore factors related to physical activity in individuals with cervical dystonia.

Methods: Subjects included in this cross-sectional study were individuals diagnosed with CD and enrolled at neurology clinics (n = 369). Data was collected using one surface mailed self-reported questionnaire. Physical activity was the primary outcome variable, measured with the Physical Activity Disability Survey. Secondary outcome variables were: impact of dystonia measured with the Cervical Dystonia Impact Scale; fatigue measured with the Fatigue Severity Scale; confidence when carrying out physical activity measured with the Exercise Self-Efficacy Scale; confidence in performing daily activities without falling measured with the Falls Efficacy Scale; enjoyment of activity measured with Enjoyment of Physical Activity Scale, and social influences on physical activity measured with Social Influences on Physical Activity in addition to demographic characteristics such as age, education level and employment status.

Results: The questionnaire was completed by 173 individuals (47 % response rate). The multivariate association between related variables and physical activity showed that employment, self-efficacy for physical activity, education level and consequences for daily activities explained 51 % of the variance in physical activity (Adj R 0.51, $F\ (5,\ 162) = 35.611$, $p = 0.000$). Employment and self-efficacy for physical activity contributed most strongly to the association with physical activity.

Conclusions: Considering the favorable consequences associated with physical activity it could be important to support the individuals with CD to remain in work and self-efficacy to physical activity as employment and self-efficacy had significant influence on physical activity level. Future research is needed to evaluate causal effects of physical activity on consequences related to CD .

Background

It is common knowledge that regular levels of physical activity are important for health-related quality of life for all individuals [1]. People with disabilities have reported worse health status than people without disabilities and receiving fewer preventive health services such as counseling around exercise habits. This is noteworthy considering the negative consequences associated with physical inactivity and a sedentary lifestyle [2]. Physical activity can be defined as all bodily movement that derives from the contraction of the skeletal muscles and results in increased energy expenditure, for example while walking, cycling or participating in sports [3]. In contrast to the large number of publications on physical activity in movement disorders such as Parkinson's disease, almost no research has been conducted on physical activity in cervical dystonia (CD), despite its possible major impact on self-perceived health and disability for the individual patient [4, 5]. Cervical dystonia is a

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neurological movement disorder with an estimated overall prevalence of 4.98 per 100 000. The disorder is characterized by excessive involuntary activity of the neck and shoulder muscles, leading to abnormal movements of the head and possibly pain [6, 7]. Although CD is generally non-progressive and limited to involuntary muscle spasms of the neck muscles the literature reveals multifaceted possible health consequences of CD. In addition to painful head and neck symptoms, disturbed sleep, limited walking, limited upper limb activity and psychosocial inconvenience have a negative impact on the patients' daily and social life, as well as employment status [8, 9]. Fatigue has been reported to aggravate the symptoms of CD and to be one contributor to the variations in disability associated with CD [10]. Botulinum toxin A is the first-choice treatment to ameliorate pain and the disabling head postures [11]. Patients experience reduction in motor impairment following botulinum toxin. However, lack of reduction in disability despite satisfaction with botulinum toxin treatment indicates the need of complementary treatment [12]. Many patients request physiotherapy. The evidence of potential benefits of physiotherapy over the short term is growing [13]. However, the therapy described is mainly focused on restoring the head position and reducing disease-related complications and not on encouraging physical activity as part of a health promoting behavior [13, 14].

Multiple factors are linked to physical activity participation. The two most consistent correlates of physical activity in adults in the general population are health status and self-efficacy [15]. Self-efficacy is defined as the confidence that one can successfully execute the behavior required to produce an outcome, such as physical activity, and is a central concept in Social Cognitive Theory [16, 17]. Another type of self-efficacy is the degree of efficacy (i.e. self-confidence) to avoid a fall, known as fall-related self-efficacy [18]. Vacherot et al. [19] concluded that CD does not affect postural control. However, in the clinical physiotherapy setting individuals with CD often report that fear of falling hinders them from performing physical activity, indicating this is a contributory factor to reduced participation in physical activities. Additionally, age, gender, and social support are correlates of activity that have been reported in the general population [15]. It has also been suggested that a feeling of enjoyment is a key construct for explaining the motivation of sport and exercise participants [20]. To our knowledge the literature on physical activity in CD is almost non-existent. The only study available indicated that the level of physical activity was associated to quality of life and health [5].

Ellis et al. [14] propose a paradigm shift in the physiotherapy treatment for patients with disabilities caused by neurologic disorders. The shift means away from a tertiary prevention approach in which the emphasis is on restoring function and reducing disease-related complications, toward a secondary preventive approach with an integration of physical activity habits in health promotion which emphasizes sustained exercise and physical activity over the course of the disease. This secondary prevention approach includes the application of evidence-based behavioral change interventions. Thus, to acquire knowledge about variables important for a physical active behavior in CD is therefore crucial.

In this pre-study it was hypothesized that demographic characteristics such as age, gender, employment status, educational level and self-perceived aspects such as symptoms and consequences of CD, fatigue, self-efficacy to physical activity, falls self-efficacy, fear of falling, enjoyment and social support for physical activity would contribute to explain reasons for physical activity in CD. The aim of the study was therefore to explore the multivariate association between a model of demographic characteristics and self-perceived aspects and physical activity in CD.

Methods

The study was performed as a cross-sectional survey with a descriptive and correlating design. One questionnaire was sent out by surface mail to all patients between 18-80 years diagnosed with CD and enrolled at neurology clinics in the region of Uppsala University Hospital, Sweden within a two weeks period in May 2011, (n = 369). Patients were excluded if they had dementia (n = 1), could not write or speak (n = 1) or were not diagnosed with CD (n = 2). All participants in the study provided written informed consent to participate. The study was approved by the Regional Ethical Review Board, Uppsala, Sweden, D-no 2010/278.

Physical activity was the primary outcome variable measured with the *Physical Activity Disability Survey – Revised* (PADS-R) [21]. This scale was used to measure self-perceived level of physical activity [22]. The scale includes six subscales; exercise, leisure time, physical activity, general activity, therapy, employment and wheelchair use for individuals with chronic illness and/or disability. For each scale the amount of physical activity during the previous week is reported. The ratings from the subscales are summed to give a total score. A higher score indicates a higher level of physical activity. No maximum score is set. For this study we divided the PADS-R scores of the group into > mean and < mean. Test-retest reliability has shown to be good [21].

The following measurements were the secondary outcome variables included in the model of self-perceived variables related to physical activity in CD.

Cervical dystonia impact scale (CDIP-58)

This scale measures the self-perceived consequences of CD using eight health categories: "head and neck symptoms", "pain and discomfort", "sleep", "upper limb activities", "walking", "annoyance", "mood" and "psychological functioning" [8]. These eight subscales correspond to three conceptual domains, namely "symptoms", "daily activities" and "psychosocial squelae". High scores indicate a high impact of CD on the individual's health. The maximum transformed score is 100. Rasch item analyses have been performed to test the validity of the scale [23]. CDIP-58 was more sensitive than comparable scales in detecting statistical and clinical changes in patients treated with botulinum toxin [24].

Fatigue severity scale (FSS)

This scale measures the perceived level of energy and severity of fatigue. A total FSS is calculated by taking the mean of all statement scores and the maximum score is 7. A higher score indicates a more severe fatigue [25]. A FSS score ≥4 can be used as a cut-off score for the presence of fatigue [26]. The English and the Swedish versions have both been found to be reliable and valid [25, 27].

Swedish version of the Exercise Self-Efficacy Scale (S-ESES)

The questionnaire includes items concerning confidence when carrying out regular physical activities and exercises. The scores are summed to give a total score of maximum 40, which indicates high self-efficacy to carry out physical activity and exercises. Satisfactory content validity as well as high internal consistency and scale integrity have been shown [28].

Falls efficacy scale (Swedish version) (FES(S))

This scale measures the degree of confidence in ability to perform common daily activities without falling [29]. The scale is divided into two subscales 1) Personal Activities of Daily Living (PADL) and 2) Instrumental Activities of Daily Living (IADL). The items can be summed to a total score of maximum 130. A high score indicates higher fall-related self-efficacy. A score of less than 80 indicates reduced self-efficacy to perform daily activities without falling. The scale has shown high test-retest reliability [30].

A question of fear of falling on a nominal level (yes or no) was included in the questionnaire, namely "Are you afraid of falling?".

Enjoyment of physical activity was measured using a scale developed by our research group. The scale used three statements for the experience of enjoyment during or shortly following physical activity of at least 10 min duration (e.g. walking): "I experience that it is fun to be physically active", "I experience a feeling of wellbeing when I am physically active" and "I feel happy with myself when I am physically active". The answers were graded on a visual scale (from 0 to 5), and were added to a total score ranging from 0 to 15, with 15 being the highest level of enjoyment.

Social Influences on Physical activity (SIPA) was used for measuring social support for physical activity [31]. The scale includes positive social influences (SIPApos) and negative social influences (SIPAneg) on physical activity. SIPApos includes questions on dimensions of companionship, informational and esteem support. SIPAneg includes questions on inhibitive, justifying and criticizing behaviours. To measure the occurrence of social influences of three different sources; family, friends and experts a 5-point scale is used. Content validity and reliability of the scale has been shown [31, 32].

Demographic characteristics were collected regarding participants' age, gender, level of education, marital and employment status, time since diagnosis, smoking and Body Mass Index (BMI).

Swedish versions were used for all instruments. PADS-R and SIPA were professional translated according to "Guidelines for the process of cross-cultural adaption of self-report measures" [33]. Psychometric properties were taken into account for all measurements except for the "Enjoyment of physical activity" scale which was developed by our research group.

Descriptive statistics of demographic characteristics were summarized. Missing values for occasional data in scales with ordinal data were imputed with the median for the appropriate subscale when the level of missing data was <33 % of the subscale. If the amount of missing data was ≥33 % no summarizing was done [34]. For the different measures this was the case in 2.9 % at most.

Distribution of data was evaluated and differences between men and women were analyzed using Chi-square tests, Mann-Whitney *U*-test or Student's *t*-test depending on the type of scale and normal distribution. Multivariate association analyses were conducted to investigate variables that might influence physical activity (dependent variable) for the whole sample, and females and males separately.

Finally, the five variables with highest β in the initial multivariate analysis were defined as the most important related independent variables. These were analyzed in an additional regression analysis in order to increase the strength of the models.

Analyses were utilizing SPSS (Statistical Package for Social Sciences, version 20). Statistical significance was set at $p \leq 05$.

Results

In total 173 individuals with CD (72.3 % female, mean age 61 years) with a median time since diagnosis of

14 years, were enrolled in the study giving a response rate of 47 %. The analysis of the non-responders (n = 181) showed a larger group of women than men, 59.2 % and 40.8 % respectively (p = 0.010). The men in the non-responders group were younger than the responders (55 ± 12 years) compared to 60 ± 10 years) ($p = 0.010$).

Demographic characteristics and secondary outcome measures are presented in Tables 1 and 2. No differences between the genders were found for most of the background variables except that more women were smokers, 26.4 % ($p = 0.037$). The female group also reported a higher level of fear of falling ($p = 0.015$), lower fall-related self-efficacy ($p = 0.043$) and higher pain and discomfort ($p = 0.031$). The mean physical activity level was 0.63 ± 1.23. Physical activity levels were lower in the female group; 68 % of the women versus 23 % of the men had an activity level less than the mean value.

The multivariate association analysis for the five most important related variables for the whole group showed that employment, physical activity self-efficacy, education level and consequences for daily activities explained 51 % of the variance in physical activity (Adj R^2 0.51, F (5, 162) = 35.611, $p = 0.000$). Employment and physical activity self-efficacy were the strongest contributors to the association with physical activity for the whole group (Table 3). When analyzing the five most important related variables for physical activity in the female group, the multivariate association analysis showed that employment, physical activity self-efficacy and education level explained 52 % of the variance in physical activity (Adj R^2 0.52, F (5, 115) =27.797, $p = 0.000$) with employment and physical activity self-efficacy the strongest contributors in the association. For the male group the analysis indicated that employment and age explained 53 % of the association (Adj R^2 0.53, F (5, 41) =10.777, p 0.000). Employment was the most strongly associated variable (Table 4).

Discussion

This study provides a new contribution to the literature in understanding what variables affect physical activity levels in patients with CD. Of the various factors studied, employment emerged as the most strongly related variable for physical activity for the total group, as well as for the male and female groups, respectively. Physical activity self-efficacy emerged as the second most strongly related variable for the total group, and also for the female group. For the male group age emerged as the second most important variable to influence physical.

Table 1 Sample characteristics with mean (SD), median (IQR), number or percent of total sample, %

Demographic characteristics	Total (n = 173)	Male (n = 48)	Female (n = 125)
Age (years)	61.1 (9.8)	61.5 (9.7)	60.2 (9.9)
Marital status			
Living alone	56 (32.7 %)	13 (27.7 %)	43 (34.7 %)
Living with partner	115 (67.3 %)	34 (72.3 %)	81 (65.3 %)
Living with children			
With children	18 (10.4 %)	9 (18.8 %)	9 (7.2 %)
Without children*	155 (89.6 %)	39 (81.2 %)	116 (92.8 %)
Education status			
Compulsory education	45 (26.3 %)	13 (27.7 %)	32 (25.8 %)
Upper-secondary education	79 (46.2 %)	23 (48.9 %)	56 (45.2 %)
Tertiary education	47 (27.5 %)	11 (23.4 %)	36 (29.0 %)
Employment status			
Unemployed	5 (2.9 %)	2 (4.2 %)	3 (2.4 %)
Employed fulltime	49 (28.7 %)	14 (29.2 %)	35 (28 %)
Retired	67 (38.7 %)	15 (31.2 %)	52 (41.6 %)
Student	11 (6.4 %)	1 (2.1 %)	10 (8 %)
Sickness benefit	37 (21.6 %)	14 (29.8 %)	23 (18.5 %)
Other	1 (0.58 %)	1 (2.1 %)	0
Time since diagnosis (years)	14 (7-21)	15 (9-21)	14 (6-20)
Smoker (yes)*	38 (22.4 %)	5 (10.9 %)	33 (26.6 %)
Body Mass Index (kg/m 2)	25.1 (22.9-28.2)	25.4 (23.5-27.5)	25.1 (22.5-28.2)

*Significant statistical difference between men and women ($p = 0.05$)

Table 2 Sample characteristics of outcome measures with mean (SD), median (IQR) or number

Outcome measure	Total	Male	Female
	n = 173	n = 48	n = 125
PADS-R			
Total	0.63 (1.23)	0.69 (1.18)	0.60 (1.25)
> mean	82	25	57
< mean	91	23	68
Subscales of CDIP-58			
Head and neck (HN)	70 (53-80)	67 (48-80)	70 (57-80)
Pain and discomfort* (PD)	58 (40-76)	48 (34-72)	60 (48-76)
Sleep (S)	45 (25-65)	42 (21-70)	45 (25-65)
Upper limb activities (UL)	50 (29-67)	43 (25-71)	51 (33-67)
Walking (W)	47 (27-71)	48 (24-66)	46 (31-71)
Annoyance (A)	45 (28-60)	35 (25-60)	48 (29-60)
Mood (M)	34 (20-51)	29 (20-49)	34 (23-52)
Psychosocial Functioning (PF)	46 (28-66)	48 (26-68)	46 (28-66)
Domains of CDIP-58			
Symptoms (HN,PD,S)	49 (30-61)	55 (41-74)	61 (48-73)
Daily activities (UL,W)	50 (31-67)	45 (26-70)	52 (33-67)
Psychosocial sequelae (A,M,PF)	42 (28-60)	38 (24-61)	42 (30-59)
FES			
Total*	124 (104-130)	128 (107-130)	120 (101-130)
Fear of falling			
Yes*	44	6	38
No	125	41	84
FSS			
Total score	4.1 (2.5-5-5)	3.8 (2.2–4.8)	4.4 (2.6–5.7)
>4	93	21	72
<4	79	27	52
Enjoyment of physical activity	14 (10-15)	12 (9-15)	14 (11-15)
SIPA (from family)	0 (0.0-0.2)	0.0 (0.0-0.3)	0.0 (0.0-0.2)

*Significant statistical differences between men and women ($p \leq 0.05$)
Note: *PADS-R* Physical Activity Disability Survey. No maximum score is set. The score is divided into < and > score. *CDIP-58* Cervical Dystonia Impact Profile (subscales and related domains), max score 100. *FES* Falls Efficacy Scale, max score 130. *FSS* Fatigue Severity Scale, max score 7. Enjoyment of physical activity, max score 15. *SIPA* Social Influences on Physical Activity. No maximum score is set

Prior findings indicate that employment status is frequently affected in CD [35]. Molho et al. [9] concluded that presence of pain was significantly associated with adverse employment outcomes and indicated a strong trend with regard to complete unemployment. Pain in CD is commonly considered a consequence or a symptom of the pathophysiological lesion, and is analyzed and treated accordingly [36–39]. Botulinum toxin treatment helps many CD patients to remain in employment [35].

Pain, measured with CDIP-58 [8] in this study, was a significantly worse symptom for the female group than for the male group. However, our findings indicate that employment status is associated with physical activity independent of the presence of pain. Being employed may contribute to physical activity on a daily basis, which may reduce pain and in so doing contribute to the possibilities of remaining in work. On the other hand, the individuals who were employed fulltime may have had less pain and less negative consequences related to CD, which this study could not identify. Questions about working conditions should be considered in future research to determine the value of working conditions in relation to physical activity levels. Our study did not include data on perceived pain relief following BTX treatment, which could be a contributing factor to the results [35]. The relationships between physical activity, pain and employment in CD need to be further investigated.

Self-efficacy is considered to be the strongest determinant of behavior, including physical activity, in the general population [40]. There is now accumulating evidence that this is also so among patients with Multiple Sclerosis [41]. This is in accordance with our results. Consequently, future research should consider developing and testing interventions that include self-efficacy as a modifiable factor to stimulate physical activity participation in CD. It is worth noting that age was not a limiting factor for physical activity for the women, but it was for the male group in this study. Older women have been shown to increase their interest in health-promoting behaviors, such as exercising [42], which could help to explain this result.

The impact of CD for the individual patient, was presented with scores from CDIP-58 [8]. Two out of the three conceptual domains of CDIP-58, representing the impact of CD on daily activities and psychosocial functioning, had higher scores, i.e. showed higher impact on health compared with scores presented earlier. The higher scores of CDIP-58 indicate that this survey rather included the individuals with higher disability due to CD than the opposite [5, 8]. However, one earlier study indicates that the severity of dystonic symptoms was not associated with an impact on either quality of life or health indicating that the severity of dystonic symptoms was not a crucial factor for quality of life, irrespective form of dystonia [5]. Other conditions such as ageing and/or medication could have deleterious effects on physical activity. Possible medications and co morbidity affecting physical activity in general and/or possible co morbidity as well as time since last botulinumoxin injection and time of completion of the

Table 3 Multivariate association analysis fo the total sample with all related independent variables for physical activity in cervical dystonia and with the five variables with highest β in the initial multivariate analyses

Independent variables	All independent variables (n = 149)		The five variables with highest β in the initial multivariate analyses (n = 168)	
	β	*p*	β	*p*
Age	-0.008	0.918		
Gender	-0.033	0.601		
Employment	-0.431	0.000*	-0.448	0.000*
Children at home	0.078	0.250		
Education	0.149	0.016*	0.136	0.016*
Symptoms	0.063	0.471		
Daily activities	-0.155	0.173	-0.146	0.032*
Psychosocial sequeale	-0.004	0.970		
Fatigue	0.003	0.968		
Physical activity self-efficacy	0.139	0.120	0.226	0.001*
Fall-related self-efficacy	0.036	0.665		
Fear of falling	0.057	0.480		
Social support (from family)	0.104	0.104		
Enjoyment of physical activity	0.107	0.124	0.096	0.113
	Adj R2 = 0.494, (F 14, 134) = 11.303, $p = 0.000$		Adj R2 = 0.509, F(5, 162) = 35.611, $p = 0.000$	

*$p = 0.05$

survey were not asked for due to the problematic way of asking this in a self-reported questionnaire and the subsequent risk of biased analyses. Treatment with botulinumtoxin reduces dystonic symptoms however, if the effect of botulinumtoxin injections is a predictor of physical activity needs to be explored.

The response rate in this study was less the 50 %. The low response rate is problematic e.g. those who did not respond may be physically less active, psychologically more inert/passive or more depressed or on the other hand not. The low response rate also limits generalization of the results for the entire CD population. However, gender and mean age of the study group was consistent with other studies describing individuals with CD [43]. The questionnaire included eight measurements. Fewer questions may have increased the chance of obtaining a higher response rate. However, this survey could not have been condensed into just a few questions, as several known variables related to physical activity had to be included [15]. The different selection of study populations in these studies (patients enrolled at neurological

Table 4 Multivariate association analyses identifying the five variables with highest β in the initial multivariate analyses for physical activity in cervical dystonia for males and females, respectively

Independent variables	Male (n = 47)		Female (n = 121)	
	The five variables with highest β in the initial multivariate analyses		The five variables with highest β in the initial multivariate analyses	
	β	*p*	β	*p*
Age	-0.247	0.052*		
Employment	-0.473	0.001*	-0.401	0.000*
Children at home			0.102	0.113
Education	0.097	0.376	0.170	0.009*
Daily activities			-0.131	0.085
Fatigue	-0.225	0.076		
Physical activity self-efficacy			0.330	0.000*
Fall-related self-efficacy	0.084	0.474		
	Adj R2 = 0.528, F(5,115) = 27.797, $p = 0.000$		Adj R2 = 0.515, F(5, 41) = 10.777, $p = 0.000$	

*$p = 0.05$

clinics vs. members of a dystonia patient association) may contribute to explaining why our study group revealed a poorer health status. Patient organizations may attract a particular subsection of the overall patient population. We argue that the representativeness was guaranteed by selection patients enrolled at a university neurology clinic and associated regional hospitals.

The mean physical activity level for the whole group, measured with PADS-R [21], was 0.63 ± 1.23 which is more than three times higher than in a sample of patients with Multiple Sclerosis, where the mean PADS-R [21] score was 0.18 ± 1.475 [44]. The comparative results may not be unexpected as CD mainly affects the neck and shoulder muscles. However, it is not yet known which value for PADS-R [21] is equivalent to the recommendations for physical activity level issued by the World Health Organization, meaning that we do not know the level of physical activity for our study group in comparison with current recommendations. No maximum PADS-R score is defined [21]. In order to understand the level of physical activity in the study group we divided the PADS-R scores [21] into scores above and below the mean.

This was a cross-sectional study, with all variables measured using a self-reporting questionnaire. Most variables represented the respondents' concepts and for that reason results were only accessible by self-reporting. Measures were chosen based on recognized reliability and validity in CD and in other chronic conditions, recommendations and clinical experience. However, the questions can be discussed. Physical activity can be objectively assessed by accelerometry [45], which should be of value for optimizing internal validity in future research. The measurement "Enjoyment of physical activity" was developed by our research group. The variable of enjoyment did not appear as a predictor for physical activity in our study group. However, the enjoyment scale consequently still lacks psychometric properties and the enjoyment results should be interpreted with caution.

Conclusions

This study highlights the fact that being employed and having physical activity self-efficacy explains a large proportion of the variation in physical activity in CD. Considering the favorable consequences associated with physical activity for all individuals it is important that the individual patient with CD is supported to remain in employment and to be physically active. However, the implications of the result must be viewed with caution due to the low response rate. To support in self-efficacy, competence in behavioral medicine is required so that cognitive behavioral strategies and medical treatment for developing personalized goals for physical activity level can be combined. Future research needs to perform tailored interventions in randomized trials to evaluate casual effects of physical activity on consequences related to CD.

Availability of supporting data

Contact the corresponding author if requested.

Abbreviations

CD: Cervical dystonia; PADS-R: Physical Activity Disability Survey – Revised; CDIP-58: Cervical Dystonia Impact Scale; FSS: Fatigue Severity Scale; S-ESES: Swedish version of the Exercise Self-Efficacy Scale; SIPA: Social Influences on Physical activity; SIPAneg: Social influences on physical activity- negative social influences; SIPApos: Social influences on physical activity- positive influences; BMI: Body Mass Index.

Unmet Needs in the Management of Cervical Dystonia

Cervical dystonia (CD) is a movement disorder which affects daily living of many patients. In clinical practice, several unmet treatment needs remain open. This article focuses on the four main aspects of treatment. We describe existing and emerging treatment approaches for CD, including botulinum toxin injections, surgical therapy, management of non-motor symptoms, and rehabilitation strategies. The unsolved issues regarding each of these treatments are identified and discussed, and possible future approaches and research lines are proposed.

Keywords: cervical dystonia, botulinum toxin, deep brain stimulation, physical therapy modalities, non-motor features

INTRODUCTION

Cervical dystonia (CD) is the most prevalent form of adult-onset focal dystonia, and is characterized by abnormal postures of head and neck, that can considerably impair daily living.

There are several unmet needs in the management of CD. In this article, we focused on four main aspects of the treatment of this disorder, including botulinum toxin injections, surgical therapy, management of non-motor symptoms (NMS), and rehabilitation strategies.

For each of these issues the state-of-the art is presented and some of the current knowledge gaps are highlighted. In addition, we propose potential research lines that could be developed to manage these issues.

BOTULINUM TOXIN

What Is Known?

Botulinum neurotoxin (BoNT) injections are the treatment of choice for CD.

There is class I evidence to support efficacy and safety of the three commercially available formulations of BoNT-A (onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA) (1–3), and of BoNT-B (rimabotulinumtoxin B) (4).

As much as 70–85% of the patients report a significant benefit from the treatment (5). Efficacy on motor symptoms varies from 20 to 70%, based on the assessing method used. Significant improvement is also documented on pain and quality of life (QoL) (6).

Although BoNT treatment is routinely performed worldwide and is satisfying for many patients, the obtained effect is still far from optimal. In addition, BoNT treatment is in some cases associated with the occurrence of side effects, such as dysphagia or excessive muscle weakness. These side effects

are due to an excessive dose of BoNT or to the spread of BoNT to adjacent structures, and may limit the efficacy of the treatment.

What Is Uncertain?

In order to further improve the efficacy and safety of the treatment, the accurate placement of the minimum effective dose of toxin in the dystonic muscles should be ensured. At present, there is still no agreement on a recommended starting dose or on the minimum effective dose per muscle.

Moreover, there is still great variability concerning treatment strategies. Multi-point BoNT injections have been proposed as more effective than single point injections (7), but convincing evidence on these topics is still lacking.

The use of polymyography to identify dystonic muscles before treatment, and the use of electromyography (EMG) to guide injections, has been proposed to improve the accuracy of BoNT delivery. While some studies show that this approach may provide a significant advantage in BoNT-naïve patients (8, 9), as well as in patients unsatisfactorily treated with standard injections (10, 11), this still need to be further confirmed in larger series. Moreover, the modalities and indications of the neurophysiological approach need to be further specified.

The use of imaging techniques has also been proposed to identify the dystonic muscles before treatment and to improve the accuracy of the placement of BoNT. Preliminary reports suggest that the use of ultrasound-guided injections might help localizing the target muscles and reducing the episodes of dysphagia in patients who had experienced it with standard treatment (12).

A number of patients do not respond to BoNT treatment, or develop a secondary resistance. A currently accepted definition of secondary non-responsiveness implies "insufficiently improved posture after three or more unsuccessful injection cycles in CD patient's previously achieving satisfactory results" (13).

Change in CD pattern across time, with the appearance of more complex multiaxial dystonic movements or tremor, account for some of the non-responders. Another well-known cause of non-responsiveness is the development of antibodies against BoNT formulations (14). This issue has been described with different BoNT formulations, including onabotulinumtoxinA, abobotulinumtoxinA, and rimabotulinumtoxinB (15), while it does not seem to be a concern when incobotulinumtoxinA is used (16). At present, there is no agreement on the strategies to avoid the formation of antibodies. Although this problem likely occurs only sporadically, a minimum safe interval of 12 weeks or longer is still used in most centers (17). This strategy, however, limits treatment of a larger number of patients, who report reemergence of symptoms before this time. The safety of shorter intervals between injections and of the so-called booster injections still needs to be explored.

Another unsolved and largely debated practical issue concerns the optimal conversion ratio between different formulation of BoNT-A, or between BoNT-A and BoNT-B.

Based on studies using different methodology, a conversion of onabotulinumtoxinA to abobotulinumtoxinA 1:3 IU (18, 19), as well as ratios of 1:2.5 (20) have been proposed over time, while a conversion ratio of 1:1 is proposed for onabotulinumtoxinA to incobotulinumtoxinA.

Future Perspectives

Future research lines should focus on improving the benefit/side effects ratio of BoNT treatment and on reducing the rate of primary and secondary non-responsive patients.

A standardized working definition of non-responsiveness should be developed, which should take into account an objective measure of the lack of improvement as well as an evaluation of the appropriateness of BoNT treatment. An objective and universally accepted working definition would be of crucial importance to assess new treatment strategies and to identify patients for whom more invasive (surgical) treatment are indicated.

Dose-finding studies and comparative studies across different toxins should be performed. The additional value of neurophysiology and imaging in improving the intramuscular placing of BoNT should be explored. In order to minimize patients' discomfort, the minimum safe interval between treatments should be determined.

SURGICAL TREATMENT

What Is Known?

Deep brain stimulation (DBS) of the internal globus pallidus (GPi) is an established surgical treatment for patients with generalized dystonia (21, 22). Because the initial studies suggested an equally beneficial effect for all body regions, the method was soon applied to patients with focal or segmental dystonias, who no longer responded to BoNT.

Krauss was the first to describe the beneficial outcome in three patients with CD in 1999 (23). Meanwhile three controlled clinical studies were conducted evaluating GPi-DBS in CD patients who failed on medical treatment: a Canadian prospective, multicenter and observer-blinded study assessed 10 CD patients who were further followed for 12 months (24). Motor improvement was 28% at 6 months and 43% at 12 months (TWSTRS motor score). Pain and disability scores were also improved by 66 and 64%, as well as mood [Beck's Depression Inventory (BDI)] and QoL (SF-36) by 58 and 24%, respectively. Another prospective single-center study followed eight CD patients for up to 48 months after GPi-DBS (25), reporting a median reduction in the TWSTRS motor score of 50% at 6 months and of 73% at last follow-up. The only randomized sham-controlled multicenter study of bilateral GPi-DBS in CD followed patients for a total of 6–9 months after surgery (26). Sixty-two patients were implanted with a neurostimulation system and randomly assigned to either active or sham stimulation (stimulator output 0V). After 3 months, TWSTRS severity score was reduced by 26% in the treatment group compared to 6% in the sham group. There was a 3.8 point difference between both groups, which was significant. TWSTRS disability score and Bain tremor score were also significantly improved in the neurostimulation group, whereas TWSTRS pain score and QoL (Craniocervical Dystonia Questionnaire-24 score) were not different. Evaluations were repeated in all patients after receiving 6 months of effective neurostimulation. At the follow-up, significant improvements compared to the pre-surgical baseline were found for TWSTRS severity score (28%), disability score (46%) and pain (51%),

Tsui score (57%), Bain tremor score (66%), and global dystonia ratings by patients (49%) or physicians (53%). BDI was reduced by 20%, the cranio-cervical dystonia questionnaire-24 showed a 28% improvement. No permanent adverse effects were found. Transient adverse effects included device infection ($n = 3$), misplacement/dislocation of electrodes ($n = 3$) or neurostimulator ($n = 1$), stroke/hemorrhage ($n = 1$), and seizure ($n = 1$). Four patients claimed pain at the extension cable. The most frequent stimulation-induced side-effect was dysarthria (seven patients). Stimulation-induced bradykinesia was observed in one patient, but has previously been described as a relevant adverse effect of pallidal neurostimulation in several series (27, 28).

It has been suggested that the subthalamic nucleus could be a better target for DBS in CD with equal motor benefit but less risk of stimulation-induced parkinsonism (29).

What Is Uncertain?

Larger series are needed to ascertain which types of CD respond best to pallidal DBS, and to assess predisposing factors and the true prevalence and risk factors of stimulation-induced parkinsonism. Subthalamic stimulation, which was forwarded as an alternative, induces (transient) dyskinesia in a large proportion of patients and the cognitive and behavioral safety has not been evaluated yet. So far, DBS has been advocated only in patients no longer responding to BoNT treatment, as a last line therapy. A comparative trial of BoNT treatment in comparison to DBS has not been performed yet.

Future Perspectives

Registry data of DBS surgery in CD would help to evaluate outcomes in daily practice, define responder profiles, and assess the frequency of less common adverse effects. The effect of DBS on non-motor features should be systematically assessed. Randomized controlled trials (RCTs) are needed to compare pallidal and subthalamic neurostimulation and DBS in general vs. best conservative management of CD.

MANAGEMENT OF NON-MOTOR SYMPTOMS

What Is Known?

Growing evidence suggests that the phenotype of dystonia includes also NMS, which could in part account for the reduced QoL in CD (30, 31).

Sensory abnormalities are the most frequently NMS associated with CD. The onset of motor symptoms can be preceded by a feeling of discomfort in the neck and dystonic movements are sometimes interpreted as an attempt to decrease this feeling (32). Involvement of the sensory system is also indicated by the *geste antagoniste*, which modifies cortical EEG activity and GPi local field potentials, even before touching the head (33). Furthermore, several studies found abnormalities in temporal and spatial discrimination thresholds in CD patients, both in affected and unaffected body parts, and in unaffected first-degree relatives (34, 35).

Pain is present in up to 90% of CD patients, which is rated as moderate to severe by 70% (36). Two-third of the patients use analgesics. Pain might be a consequence of motor symptom severity (37), but could also be influenced by depressive and anxiety symptoms (31). It is proven that BoNT treatment as well as surgical treatments, such as DBS (26) or selective peripheral denervation (38), significantly improves pain associated with CD (36, 37).

The prevalence of psychiatric disorders in CD can reach up to 91.4%, compared to 35% in the general population (39). This could logically be the consequence of living with a chronic, visible, and invalidating disorder. However, compared to the prevalence of psychiatric symptoms in other chronic and visible diseases, such as alopecia areata, CD patients still have a significantly increased odds ratio to develop psychiatric co-morbidity (40). The most prevalent psychiatric disorders include depressive symptoms (40–45), anxiety symptoms/panic disorders (39, 40, 44, 45), obsessive–compulsive symptoms (41, 45) and substance abuse (45). Importantly, a few studies showed that psychiatric co-morbidity is the most important predictor of poorer health-related QoL, especially for the domains general health, role functioning, bodily pain, and emotional and mental health (31, 46, 47).

At this moment, no treatment trials have been described with the aim to directly improve psychiatric symptoms in CD patients.

What Is Uncertain?

The prevalence and characteristics of the different NMS in CD, including sleep disturbances and cognition, have not been systematically studied and existing studies show contrasting results. A recurring debate is whether NMS are a direct consequence of the motor symptoms of dystonia or intrinsic to the neurobiology and thereby part of the phenotype.

Cervical dystonia patients showed an impaired sleep quality compared to healthy controls: in two studies, this was correlated with depressive symptom scores (48, 49), while in one study it appeared to be independent from psychiatric disorders and medication use (50). Successful BoNT treatment did not improve sleep quality, arguing against a secondary discomfort due to the dystonia motor symptoms (50). Excessive daytime sleepiness was detected in one study, but at least in part explained by the use of anticholinergic drugs (51). Other studies did not find significant differences in daytime sleepiness (48, 49).

Studies concerning cognitive impairment in CD are still very limited. One study showed impairments in the domains working memory, processing speed, visual motor ability, and short-term memory (52). Other small studies found impairment of visuospatial function (53) and a sustained attention deficit, the latter disappearing after BoNT treatment (54).

Convincing data support a disruption of sensory-motor system also in healthy first-degree relatives of dystonic patients, suggesting a possible endophenotype (55). For example, temporal discrimination threshold (TDT) was found abnormal not only in about 80% of dystonia patients but also in about 50% of first-degree female relatives older than 48. In male relatives, the penetrance was reduced (34, 56).

The onset of psychiatric disorders before the onset of the movement disorder in ~70% of the cases (42, 44, 45) is one of

the strongest arguments toward a shared pathophysiology. This is also supported by a men-to-women ratio of psychiatric disorders of 1:1 in CD patients compared to 1:2 in the general population, higher incidence of psychiatric disorders in CD patients compared to other visible and chronic disorders, and different personality profiles found in CD patients, which develop long before adolescence and onset of motor symptoms (35).

Drawing firm conclusions on the etiology of NMS in CD remains difficult, also considering the tight correlation between pain, psychiatric symptoms, sleep disturbances, and motor symptoms.

Future Perspectives

In order to solve the issue of the etiology of NMS in CD, prospective studies are necessary. Selecting an appropriate group for prospective studies has proven challenging. This might change with the identification of genetic forms of CD, such as the *GNAL* and *ANO3* gene (57–60), which would allow studying homogeneous clinical subgroups, even in the pre-symptomatic phase.

Another strategy could be the identification of endophenotypes in larger groups, based on biomarker, such as the TDT.

Clinical trials are required toward the effect of treatment of NMS on health-related QoL.

REHABILITATION STRATEGIES

What Is Known?

Evidence toward the effectiveness of rehabilitation strategies is scarce. Two systematic reviews described the effects of different rehabilitation strategies in various forms of primary dystonia (61) and CD alone (62), suggesting that multimodal physical therapy (PT) programs, added to BoNT treatment, further improve disability and pain compared to BoNT treatment alone (61, 62). Only three clinical trials (63–65) and one case–control study (66) investigated the effects of a multimodal PT program in combination with BoNT treatment.

One single-blind RCT in 40 patients showed significant improvements on pain and daily-life activities, and a prolonged duration of the BoNT effect, after a 6-week PT program of active exercises, muscle stretching and massage compared to BoNT treatment alone (63). A second single-blind RCT in 40 patients showed decreased disability and a significant decrease of head deviation and improved hand functions after a 6-week PT program of active exercise, muscle stretching, and TENS in addition to BoNT treatment (64). The third single-blind RCT of 20 patients found only a trend toward greater improvement on head posture, pain, and disability in the group that received 12 weeks of active exercise, relaxation, and BoNT treatment compared to the group that received relaxation and BoNT treatment only (65).

One case–control study followed 40 patients in a 4-week PT program of active exercise, muscle stretching, active and passive neck mobilizations, and electrostimulation of the dystonic muscles in adjunction to BoNT treatment, or BoNT treatment alone. The PT group showed significantly more improvement on pain, and on some subscales of the SF-36 (66).

What Is Uncertain?

The available results should be interpreted with caution. The content of PT programs varied across studies, including motor learning exercises [Bleton method (67)], passive or active mobilization techniques of the cervical spine, stretching of the dystonic muscles, relaxation, and electrotherapy, such as EMG biofeedback or TENS. It is, therefore, difficult to identify the most effective intervention or combination of interventions.

Frequency and duration of PT sessions also varied from 40 min every other day for 6 weeks (64), 75 min 5 days a week for 5 weeks (66), 90 min a day for 2 weeks (63) up to a 12-week program with a weekly 30-min session during the first 4-weeks, and a session every fortnight for the remaining 8 weeks (65). Besides, current studies mainly show short-term effects associated with brief and intensive PT programs (63, 64, 66), which could be difficult to implement in current regular care of a chronic disease, such as CD. The long-term effects of less intense and longer PT programs have not been explored yet.

Future Perspectives

Future research should focus on standardized PT programs that are effective but also adequate to treat patients with a chronic conditions and an active life. PT programs with longer treatment periods and the emphasis on self-management of symptoms and the ability of patients to improve their performance of daily life tasks should be the focus. Currently, such a PT program is being investigated in a large Dutch RCT (68).

The effect of PT interventions on the pathophysiological mechanisms of CD should also be studied. Although the pathophysiology of CD remains largely unclear, maladaptive neuroplastic changes may play an important role (69). By integrating PT programs with modern training principles that have proven relevant for neural rehabilitation and motor learning, these deficit may be altered (70–74).

Additionally, high-quality research combining electrophysiological parameters or imaging techniques with clinical outcomes can help to further unravel the effects of PT programs on CD.

FINAL CONSIDERATIONS

There are still many unmet needs in the management of CD. A better understanding of the pathophysiology of CD is necessary to plan new treatment strategies and to improve existing treatments. In addition, the available rating scales for CD have some clinimetric issues and do not equally address all the domains of the disease. This points to a need for updated scoring instruments in order to support studies on the pathogenesis and progression of the disease and to more accurately evaluate the outcomes of clinical trials. Specific standardized rating scale for NMS in (cervical) dystonia should also be developed.

Finally, it is widely accepted that motor improvement is not the only determinant of treatment success in CD: pain, social distress, and psychological factors play sometimes a greater role toward patient satisfaction. This calls for a multi-disciplinary approach posing more attention to the subjective determinants of QoL in CD.