

Nonmotor Manifestations of Dystonia: A Systematic Review

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ABSTRACT: Nonmotor symptoms are increasingly recognized as important determinants of quality of life and disability in a wide range of movement disorders. There is a limited body of research suggesting that many of these symptoms are also commonly associated with primary and other genetic forms of dystonia. However, the significance, etiology, pathophysiology, and treatment of these symptoms remain poorly described. The following is a review of the literature

that focuses primarily on the association of these types of dystonia with psychiatric disorders, cognition, sleep, pain, and autonomic symptoms. We will also discuss potential mechanisms and approaches to treatment for nonmotor features of dystonia. © 2011 Movement Disorder Society

Key Words: dystonia; nonmotor; depression; anxiety; cognition; pain; sleep

Nonmotor symptoms are increasingly recognized as an important determinant of quality of life (QOL) and disability in movement disorders. Nonmotor symptoms include alterations of mood, cognition, sleep, autonomic function, and/or pain that cannot be directly attributed to a secondary consequence of motor symptoms. These symptoms are described most commonly in Huntington's disease¹ and Parkinson's disease (PD),² but have also been reported in other movement disorders including dystonia.^{3,4}

The etiology of dystonia can be either primary or secondary. In primary dystonia, no abnormality is present other than the dystonia itself. Secondary dystonia is the result of neurodegenerative disease, metabolic disorders, or other acquired causes.⁵ Dystonia-plus syndromes are inherited forms of secondary dystonia that are accompanied by other neurologic

abnormalities. These, as well as other heterogeneities in dystonia populations, make for significant challenges in assessing nonmotor symptoms across studies that may sample very different patient populations.

Although psychological and other nonmotor symptoms have been reported to occur in primary and other genetic forms of dystonia, their significance and causes are still debated. This article will summarize the current literature on this topic, review the potential relationship to pathophysiological data, and finally suggest areas where further research is needed.

Methods

A search strategy was used to reference English-language articles in Medline from 1966 to December 2009. A total of 1902 records were retrieved, and the abstracts were reviewed. In the absence of an abstract, the title was considered. Studies were included if the participants had primary dystonia or dystonia-plus syndromes and if the focus was related to nonmotor symptomatology. Reference lists of all initially included studies were searched for additional publications. Search terms were selected based on common nonmotor features of other movement disorders (ie, PD) and terms associated with mood disorders, the category of nonmotor symptoms that has been studied most thoroughly in dystonia. The following search terms were used: dystonia, torticollis, dysphonia,

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blepharospasm, depression, bipolar, mood, anxiety, psychiatric, substance abuse, phobia, personality, deep brain stimulation, anticholinergic medications, neuroimaging, psychosis, hallucinations, memory, cognition, neuropsychology, sleep, fatigue, energy, pain, autonomic, sweating, blood pressure, orthostatic, constipation, urinary, urination, sexual, erectile.

Results

Mood (n = 25 Studies)

There are numerous reports in the literature indicating that patients with primary and other genetic forms of dystonia have higher than expected rates of depression and anxiety (see Table 1). The prevalence of depression and anxiety in patients with dystonia varies based on the study and on sample size, but cohorts analyzed in this article indicate that 12%–71% of patients with focal or generalized dystonia suffer from depression and anxiety over the course of a lifetime, with most studies falling in the range of about 25%–50%. This percentage is similar to that for Parkinson's disease, which also disturbs frontal-subcortical circuits.^{6,7} It is increased compared with those who are healthy^{8–11} and those with other medical conditions.^{12–14}

There is conflicting epidemiological evidence about whether depression and anxiety are secondary to motor manifestations and subsequent psychosocial impairment or are a primary feature of the disease. On the one hand, studies have reported a higher pre-morbid incidence of depression and anxiety in patients with dystonia,¹⁵ suggesting that, similar to PD, this may be an independent manifestation of dystonia. In addition, a study of manifesting and nonmanifesting carriers of the *DYT1* gene showed that carriers (with or without symptoms) had a significantly higher rate and earlier onset of major depressive disorder than noncarrier controls.¹⁰ Although these studies may have been prone to recall bias, they suggest that the underlying pathophysiology of dystonia may predispose patients to mood disorders. Striatofrontal circuits that help regulate mood and behavior have been shown to be disordered in dystonia patients based on functional imaging^{16–18} and may act as a pathologic substrate. Functional imaging studies have shown that these nonmanifesting carriers have decreased D2 receptor binding in the basal ganglia and hypermetabolism in the putamen, anterior cingulate, and cerebellar hemispheres.^{19,20} Patients with GTP cyclohydrolase deficiency (*DYT5* dystonia) may also have higher rates of depression than the general population, perhaps because of reduced conversion of tryptophan to serotonin.²¹

There is mixed evidence to suggest that depression and anxiety symptoms are associated with disease

severity, with some studies showing correlation^{7,22,23} and others no correlation.^{9,24} Of note, a 2-year longitudinal follow-up of patients with spasmodic torticollis showed that changes in the severity of the dystonia were closely linked to subsequent changes in mood, disability, and body concept.^{14,25} Other factors that have been correlated with higher depression scores include marital status (higher scores for separated/divorced patients) and body parts affected (higher scores for cervical dystonia versus spasmodic dysphonia or hemifacial spasm).²² Self-esteem, body concept, and QOL have also contributed to the variance of depression.²² Finally, the degree of psychopathology may also be associated with triggering events. Scheidt et al reported that cervical dystonia patients were more likely to have psychopathology if symptoms were triggered by a stressful life event.²³

Deep brain stimulation (DBS) of the internal globus pallidus, an emerging procedure for selected primary dystonias, deserves special attention for its effect on mood. Although most studies suggest that DBS for dystonia results in mildly improved or unchanged measures of depression,^{26–29} worsened mood and suicide have also been reported.^{30,31} The majority of these patients had a previous history of depression or other risk factors for suicide prior to surgery. Interestingly, most of the patients who committed suicide also had an excellent motoric response from stimulation, providing further evidence that severity of dystonia may not correlate with symptoms of low mood.

In dystonia, dysfunctional mood is one of the most important predictors of a patient's QOL.²⁵ We recently reported the results of a large retrospective case series of patients with dystonia who were given questionnaires assessing QOL, depression, anxiety, and other mood variables.⁴ Both physical and mental aspects of QOL were strongly associated with depression and anxiety. Treatment of the motor symptoms of dystonia may or may not^{32–34} lead to improvement in depression and health-related QOL. Other factors in addition to motor symptoms—long-standing disability, pain, deformity, and lifestyle changes—may also contribute to depression and poor QOL.

Several areas of future research may prove useful. Routine screening of patients with dystonia, or those who have genetic mutations predisposing to dystonia, for depression and anxiety would seem to be warranted. Development of a nonmotor screening tool for patients with dystonia could make this process more efficient. Identifying those who are most at risk for mood dysfunction would be helpful to the clinicians caring for these patients. For instance, does the side of motor symptom onset make someone more likely to develop depression with their dystonia? Studies in the healthy brain indicate that the right forebrain plays a large role in mood processing.³⁵ Also, patients with left-sided onset of their parkinsonian motor symptoms

TABLE 1. Depression/anxiety studies in dystonia

Author, year	Study type	Sample size	Findings	Comments
Aronson, 1968 ⁷⁷	Case-control	31 Spasmodic dysphonia 50,000 Controls (general outpatient medical population)	No statistically significant difference between the 3 groups on MMPI	
Van Hoof, 1987 ⁷⁸	Retrospective case-control	18 Psychogenic aphonia 17 Spasmodic torticollis	No difference in personality inventory; 2 of 17 spasmodic torticollis patients had depression	
Harrington, 1988 ⁷⁹	Retrospective case-control	Healthy controls (unspecified) 22 Writer's cramp 22 Healthy controls	No difference in anxiety indices; 3 subjects had symptoms of generalized anxiety.	
Naber, 1988 ³	Case-control	32 Spasmodic torticollis 32 Controls with Parkinson's disease	MMPI scores, specifically hypochondriasis, depression, and hysteria, were elevated in 50% of patients	MMPI scores correlated with severity of neurologic symptoms and were similar to PD controls
Jahanshahi, 1988 ¹²	Case-control	100 Spasmodic torticollis	No difference in MMPI, anxiety, or obsessive symptoms	7 ST patients with prior psychiatric histories were excluded
Jahanshahi, 1989 ⁸¹	Case series	49 Controls (cervical spondylosis) 61 Spasmodic torticollis	36% had normal MMPI profiles; conversion "V" profiles were seen in 9%	58.5% had MMPI pattern consistent with mild depression
Jahanshahi, 1990 ¹⁴	2-Year longitudinal cohort	67 Spasmodic torticollis	25% of patients depressed at both times	Depression improved in patients with successful Botox treatment
Jahanshahi, 1990 ³² Jahanshahi, 1988 ⁸⁰	Retrospective case-control	85 Spasmodic torticollis 49 Controls (cervical spondylosis)	ST patients had higher prevalence (54%) and severity of depression, disability, and negative body concept.	Body image, neuroticism, pain, and disability correlated with depression
Grafman, 1991 ²⁴	Case series	20 Focal hand dystonia	Four of 20 had mild depression, 30% with elevated anxiety inventory scores.	MMPI and psychiatric histories were unremarkable and did not correlate with dystonia severity
Cannito, 1991 ⁸	Retrospective case-control	18 Spasmodic dysphonia 18 Healthy controls	SD had higher rates of clinical depression and anxiety (both 39%)	
Jahanshahi, 1992	Longitudinal cohort	26 Spasmodic torticollis	Improved depression and disability after Botox injections in 22 patients whose torticollis improved.	Body concept also improved but not significantly
Murry, 1994 ¹¹	Case-control	32 Spasmodic dysphonia 28 Healthy controls	SD had higher ratings of depression, state and trait anxiety	Improvements noted in depression and anxiety following Botox treatment
Scheidt, 1996 I-IV ²³	Retrospective case-control	256 Spasmodic torticollis HC (unspecified)	27% of ST patients had psychopathology including 23% with clinical depression	Depression correlated with severity
Wenzel, 1998 ³⁹	Case series	44 Spasmodic torticollis	High lifetime prevalence of psychiatric disorders (66%) especially anxiety disorders (34%), including panic disorder (20%) and MDD (25%)	43% of patients reported psychopathology preceded motor symptoms
Gundel, 2001 ⁹	Case-control	116 Spasmodic torticollis 483 Healthy controls	Higher lifetime prevalence of MDD (46%) and anxiety d/o, especially social phobia (71%)	Psychopathology did not correlate with dystonia severity; social phobia correlated with body image
Morar, 2002 ¹⁵	Case series	40 Spasmodic torticollis	40% with anxiety, 37.5% with major depressive disorder	Criteria for 1 lifetime psychiatric diagnosis fulfilled prior to onset of ST in 42.5%
Muller, 2002 ³³	Longitudinal cohort	131 Spasmodic torticollis 89 Blepharospasm	47% depression in ST patients, 37% in BL patients; health-related QOL significantly worse in all domains compared with controls	Botox improved clinical symptoms but minimal improvement in health-related QOL

TABLE 1. (Continued)

Author, year	Study type	Sample size	Findings	Comments
Gundel, 2003 ¹³	Retrospective case-control	48 Spasmodic torticollis 48 Controls (alopecia areata)	Higher prevalence of psychiatric diagnosis (77%) including anxiety (69%) and mood (19%) disorders	Social phobia (54%) was the most common anxiety disorder
Heiman, 2004 ¹⁰	Case control	96 Manifesting carriers of DYT1, 60 Nonmanifesting carriers of DYT1 65 Noncarriers	Risk for recurrent major depressive disorder increased in both NMC (RR, 4.95) and MC (RR, 3.62) compared with noncarriers	Mutation carriers also had earlier onset depression than noncarriers
Lauterbach, 2004 ⁶	Retrospective case control	28 Primary generalized dystonia and spasmodic torticollis 1:128 Matching with healthy controls 329 Focal and generalized dystonia	Higher prevalence of MDD (25%), BMD (7%), phobias (39%), GAD (25%), and alcohol abuse (11%) than in HC 30% reported moderate to severe depression; disfigurement, negative body concept, low self-esteem, and QOL were important contributors to depression	53% of dystonia patients were on GABA agonists; phobias and GAD frequently preceded motor symptoms
Lewis, 2008 ²²	Case series			

BL, blepharospasm; BMD, bipolar mood disorder; FHD, focal hand dystonia; GAD, generalized anxiety disorder; HC, healthy controls; MC, manifesting carriers; MDD, major depressive disorder; MMPI, Minnesota Multiphasic Personality Inventory; NMC, nonmanifesting carriers; PA, psychogenic aphonia; PD, Parkinson's disease; PG, primary generalized dystonia; QOL, quality of life; SD, spasmodic dysphonia; ST, spasmodic torticollis; WC - writer's cramp.

may have more prominent mood and pain symptoms.³⁶ Last, studies utilizing more standardized scales of depression and anxiety would clarify the true incidence of mood disorders and make comparisons easier.

Other Psychiatric Disorders and Symptoms (n = 10)

A small group of studies have looked specifically for obsessive-compulsive symptoms in dystonia (see Table 2). In 1 of the larger cohorts, 19.7% of patients with idiopathic focal dystonia met DSM-IV criteria for obsessive-compulsive disorder.³⁷ This percentage is slightly higher than that in other studies reviewed.^{15,38,40} No significant differences in obsessive-compulsive symptoms emerged in a study comparing DYT1 carriers with a control population.⁴⁰ In contrast, symptomatic carriers of *DYT11*, the gene for myoclonus-dystonia, had a higher rate of obsessive-compulsive symptoms than asymptomatic carriers and control populations.^{38,41}

Alcohol abuse and dependence has been reported in the *DYT11* mutation (myoclonus-dystonia) as well as in idiopathic generalized and focal dystonia, albeit to a lesser extent. In *DYT11*, a study of carriers versus noncarriers revealed no significant differences in alcohol dependence. However, some^{38,41} but not all⁴² studies have shown that symptomatic carriers demonstrate more alcohol dependence than unaffected carriers. Given the typical sensitivity of myoclonus to alcohol, the alcohol dependence seen in certain patients may be the result of alcohol's symptomatic effects rather than a manifestation of the gene itself.³⁸ Aside from the connection to *DYT11*, alcohol abuse was found to be significantly higher than healthy controls in a small cohort of patients with primary generalized dystonia and spasmodic torticollis.⁶

Social phobia in dystonia is often comorbid and associated with other anxiety symptoms. In 1 larger study of 116 patients with spasmodic torticollis, a 71% lifetime prevalence of social phobia was found by using the Social Phobia and Social Interaction Anxiety scales.⁹ This prevalence correlated with body image and a "maladaptive attitude" toward their illness, not with the objective severity of the dystonia.⁹ It can be hypothesized that self-esteem and body concept play an important role in the development of social phobia, much like depression and other forms of anxiety.

Screening for these conditions in patients with dystonia is of great importance. This is particularly true with the association of alcoholism in patients with DYT11 dystonia. Physicians should consider counseling patients, specifically adolescents, about the risks of using alcohol to treat their symptoms. Further research verifying the possible association between

TABLE 2. Obsessive compulsive symptoms

Author, year	Study type	Sample size	Findings	Comments
Mearns, 1971 ⁸²	Case-control	32 Spasmodic torticollis Healthy controls (unspecified N)	ST had higher than expected obsessional personality traits but not symptoms.	Obsession correlated with neuroticism.
Bindman, 1977 ⁸³	Case series	10 Writer's cramp	9 of 10 WC had obsessive personalities.	
Mathews, 1978	Case series	29 Spasmodic torticollis	Neuroticism, obsessional symptoms, introjective hostility unchanged from general population.	23 of 29 with "adverse social effects" and 9 of 21 with moderate-severe marital discord Did not assess for clinical OCD.
Bihari, 1992 ⁸⁴	Retrospective case-control	21 Blepharospasm	BL patients had higher scores on obsessive-compulsive inventory.	
Broocks, 1998 ⁸⁵	Case series	19 Healthy controls 13 Blepharospasm	Significantly more obsessive-compulsive symptoms in BL group than in HFS group.	
Kubota, 2001 ⁸⁶	Retrospective case-control	13 Hemifacial spasm 12 Writer's cramp 12 Disease control (including CTS)	WC had significantly higher obsessive compulsive symptoms score than either control group	There were no differences between diseased and healthy controls.
Cavallaro, 2002 ⁸⁷	Case series	12 Healthy controls 76 Idiopathic focal dystonia	19.7% satisfied DSM-IV criteria for OCD; morbidity risk for first-degree family members of OCD patients was 13.8%, significantly higher than general population	
Heiman, 2007 ⁴⁰	Case-control	96 Manifesting carriers of DYT1 60 Nonmanifesting carriers of DYT1	No difference in OCD or obsessive-compulsive symptoms between controls and carriers.	First study examining OCD specifically in DYT1 carriers
Saunders-Pullman, 2002 ³⁸	Case-control	65 Healthy controls 16 Manifesting carriers of DYT11 11 Nonmanifesting carriers of DYT11	Rate of OCD higher in carriers (5 of 27) than non-carriers (0 of 28) and greater in symptomatic (4 of 16) than in nonsymptomatic (1 of 11)	
Hess, 2007 ⁴¹	Retrospective case-control	28 Noncarriers 20 Manifesting carriers of DYT11 10 Nonmanifesting carriers of DYT11 34 Healthy controls	Increased rate of OCD, EIOH dependence among MC group, not NMC group	

BL, blepharospasm; CTS, carpal tunnel syndrome; HC, healthy controls; HFS, hemifacial spasm; IFD, idiopathic focal dystonia; MC, manifesting carriers; NMC, nonmanifesting carriers; OCD, obsessive-compulsive disorder; QOL, quality of life; ST, spasmodic torticollis; WC, writer's cramp.

different types of dystonia and alcoholism is needed. Also lacking from the literature are studies assessing the incidence of other psychiatric disorders (ie, bipolar disorder) in dystonia patients.

Cognition (n = 14)

Several studies of cognition have been performed in both idiopathic and genetic forms of dystonia (see Table 3). By using detailed neuropsychological testing, many of these studies have shown statistically significant (albeit, at times subtle) deficits in executive, attentional, or visuospatial function. From the available evidence, it is unclear how functionally significant these deficits are. That certain findings such as impaired sequence learning are not consistently replicated suggests that the severity of these findings may be mild. There are several limitations of the current literature regarding cognition, including small sample sizes. Also notable is the variability of several factors, including age, education level, premorbid cognitive function, type of dystonia, and antidystonic medication burden at the time of testing. The studies that accounted most thoroughly for these confounding factors showed either no difference between dystonia patients and controls or only mild executive dysfunction including set-shifting deficits, verbal learning, category fluency, and performance of dual tasks.^{43–46}

The etiology of these cognitive deficits is not entirely clear. One possible explanation is that antidystonic medications play a part, particularly if a patient is on an anticholinergic agent or on a benzodiazepine. Although patients in several of these studies were on medications at the time of testing, there has not been clear evidence that medications are directly causative. Chronic exposure to anticholinergic medications affected performance on a memory task in 1 study of adult patients with dystonia.⁴⁷ Another study showed that cognitive processes were only mildly affected by anticholinergic medication, and this was only in elderly patients.⁴⁸ Three of 23 pediatric patients reported being forgetful in an early study using high-dose benzhexol therapy for dystonia.⁴⁹

Another possibility is that concurrent mood disorders may lead to impairments in executive function. Depression causing a “pseudodementia” is well established as a diagnostic consideration in patients with untreated low mood. Moreover, patients with OCD are known to have deficits in organizational strategies and executive dysfunction.⁵⁰ Although disorders of mood have not been definitively linked to cognitive dysfunction in dystonia, 1 recent study showed a possible association between executive dysfunction in patients with idiopathic focal and segmental dystonia and obsessive compulsive symptoms.⁴⁵

A third potential mechanism for cognitive impairment is the possibility that the disabling symptoms of

dystonia, including pain, are impairing attentional processes. In a small sample of patients with primary cranial dystonia, sustained attention deficits were shown to improve following botulinum toxin injections, suggesting that dystonic activity may impair attentional processing.⁵¹ Executive function also improved mildly but significantly in a group of generalized dystonia patients after undergoing GPi DBS surgery.⁵²

Although secondary effects of motor symptoms may be partly to blame, there is evidence to suggest that asymptomatic carriers of DYT1, the most common form of genetic dystonia, also have mildly impaired cognition and abnormal functional imaging, particularly in motor and visual sequence learning.^{21,53} Functional imaging studies in this population have shown compensatory overactivation of the lateral cerebellum and right inferotemporal cortex with a lack of recruitment of prefrontal regions, which may be a result of underlying frontostriatal dysfunction.¹⁶

Additional studies of cognition in dystonia that control for factors such as medication burden and mood symptoms are needed. Studying cognitive deficits in specific forms of dystonia without combining dystonia subtypes would also be helpful. In addition, it is unclear how medications for dystonia could potentially affect cognition in the long term. Anticholinergics, frequently used for symptomatic treatment of dystonia, can cause delirium in the short term and likely lead to cognitive impairment in the elderly and memory-impaired.^{54,55}

Sleep and Energy (n = 13)

There are relatively few articles addressing sleep in patients with dystonia. Recent studies have focused on patient surveys in order to measure quality of sleep and symptoms of sleepiness. In patients with blepharospasm and cervical dystonia, quality of sleep was impaired in both groups using the Pittsburgh Sleep Quality Index.⁵⁶ Differences seen in the cervical dystonia group, however, were partly confounded by higher scores on the Beck Depression Inventory. Excessive daytime sleepiness, using the Epworth Sleepiness Scale (ESS), was not found to be significantly more frequent when compared with a group of control subjects. In contrast, another study specifically evaluating daytime sleepiness (again using the ESS) found that a significantly higher percentage of patients with cervical dystonia had scores > 11 when compared with patients with other focal movement disorders or to age-matched controls.⁵⁷

Although there is mixed evidence that dystonia leads to sleepiness, several studies suggest that either sleep structure or quality is impaired. Specific polysomnographic abnormalities have been reported, including problems with sleep initiation and maintenance,

TABLE 3. Studies of cognition in dystonia

Author, year	Study type	Sample size	Findings	Neuropsychological tests	Comments
Eldridge, 1970 ⁸⁷	Case-control	14 Autosomal recessive dystonia 10 Siblings 24 Controls	Statistically significant increase in IQ scores for patients affected with autosomal recessive dystonia	IQ test	
Taylor, 1991 ⁴⁸	Case-control	20 Idiopathic focal dystonia 20 Healthy controls	Only explicit memory, speed of information processing affected by high-dose anticholinergics	NART, WAIS-R, LP, VR, DRT, TT, BSRT, CALT, BC, Item 99 from LNNB, SCWT, VFT, WCST	Vulnerability to meds highly age dependent
Hinse, 1996 ⁸⁸	Case-control	15 Spasmodic torticollis 15 Normal controls	ST patients performed significantly worse on spatial tasks requiring mental manipulation of personal space	MW, HRDT, CBTT, VST	No significant difference in spatial perception
Ghilardi, 1999 ⁵³	Case-control	4 Nonmanifesting carriers of DYT1 5 Healthy controls	NMC patients had significantly decreased scores for motor and visual sequence learning compared with HC group	ME, MSL, VSL	
Ghilardi, 2003 ¹⁸	Case-control	12 Nonmanifesting carriers of DYT1 (no history of psychiatric disease) 12 Healthy controls	Sequence learning impaired in carriers with preserved motor performance	CCW, RAN, SEQ	Overactivation of left PMC, right SMA in NMC patients during sequence learning (PET scan); may be compensating for striatal dysfunction
Jahanshahi, 2003 ⁴⁶	Case-control	10 Idiopathic focal dystonia + idiopathic generalized dystonia 12 Healthy controls	Significant difference in category fluency and performing dual tasks; otherwise, preserved executive function compared with controls	NART, WFT, WCST, SCWT, MDT, SORNS, RNG, WICAL, PVSAT, DIP	Only 1 of 10 patients on medications (4 mg Artane/day); dystonia group had nonsignificant increase in self-reported depression
Scott, 2003 ⁸⁹	Case series	14 Primary dystonia (7 men, 7 women) prior to undergoing GPI deep brain stimulation surgery	Baseline impairment with extradimensional set shifting (prior to DBS surgery), part of CANTAB battery	CANTAB, NART, Raven, SDMT, Stroop, TM, BNT, JLO, SCOLP, RMT, AMIPB, DS, CF	Not clear if this impairment is functionally significant or if it improves with GPI surgery; study not controlled for mood, pain, medications
Balas, 2006 ⁴⁴	Case-control	20 Manifesting carriers of DYT1 8 Nonmanifesting carriers of DYT1	Symptomatic patients performed better on semantic verbal fluency test, worse on verbal learning test	Raven, RAVLT, RCF, PVF, SVF, TMA/B, Stroop, CANTAB, WAIS-III, JLO, PP	No difference between nonsymptomatic carriers and controls; statistically accounted for medications, anxiety levels
Pillon, 2006 ⁵²	Longitudinal cohort	28 Matched controls 22 Primary generalized dystonia undergoing DBS surgery	No presurgical cognitive decline in executive function; GPI DBS mildly but significantly improved executive function	Raven, WAIS-R, GBT, WCST, VFT, TMA/B	Improvement either related to DBS or reduction in anticholinergic drugs 20 of 22 patients on medications prior to surgery

TABLE 3. (Continued)

Author, year	Study type	Sample size	Findings	Neuropsychological tests	Comments
Allam, 2007 ⁵¹	Case-control	9 Primary cranial dystonia (blepharospasm) 9 Healthy controls	Sustained attention deficits prior to Botox injections; following injections, no significant difference in sustained attention compared with controls	RAVLT, TPT, DSub, DSY, SCWT	Executive dysfunction may be related to disrupting effects of symptoms
Bugalho, 2008 ⁴⁵	Case-control	45 Idiopathic focal/segmental dystonia 27 Healthy controls	More set-shifting deficits in dystonia group, also had significantly more obsessive compulsive symptoms	WCST, SCWT, BAT, BVRT	No patients on anticholinergic medication
Carbon, 2008 ¹⁶	Case-control	6 Nonmanifesting carriers of DYT1 6 Healthy controls	NMC patients performed at control levels during sequence learning	TSEQ, CCW	NMC patients overactivated lateral cerebellum, right inferotemporal cortex, underactivated prefrontal regions
Aleman, 2009 ⁴³	Case-control	20 Blepharospasm 17 Healthy controls	BL patients showed impairment of complex movement planning, motor dexterity, visuospatial working memory, and tactile object recognition	WAIS-III, FDT, Raven, LT, LOW I/II, SL, WCST, PP, OMT, DR, TD, Tap	Groups matched for severity of depression and education level

AC, anticholinergic; BC, Block Counting Item from Stanford-Binet Intelligence Test; AMIPB, Adult Memory and Information Processing Battery; BAT, Block Assembly Test of WAIS; BL, blepharospasm; BNT, Boston Naming Test; BSRT, Buschke Selective Reminding Test; BVRT, Benton Visual Retention Test; CALT, Conditional Associative Learning Test; CANTAB, Cambridge Neuropsychological Test Automated Battery; CBTT, Corsi's Block Tapping Test; COW, matched motor baseline task; CF, Medical College of Georgia Complex Figures; CLTR, Consistent Long-Term Memory; DR, Digital Recognition; DRT, Delayed Recognition Span Test; DS, digit span; DSub, Digit Subtest of Wechsler Memory Scale-R; DSY, Digit Symbol subtest of the Wechsler Intelligence Scale-R; DTP, dual task performance; FDT, Five Digits Test; GBT, Grober and Buschke test; HC, healthy controls; HRDT, Hebb's Recurring Digits Test; IFD, idiopathic focal dystonia; IGD, idiopathic generalized dystonia; JLO, judgment of line orientation; LNNB, Luria-Nebraska neuropsychological battery; LOW I/II, List of Words I and II; LP, Logical Passages; LT, Luria task; MC, manifesting carriers; MDT, missing digit test; ME, motor execution; MSW, motor sequence learning; MW, Mehrfachwahl-Wortschatztest; NART, National Adult Reading Test; NMC, nonmanifesting carriers; OMT, Oral Making Trails; PET, positron emission tomography; PMC, premotor cortex; PP, Purdue pegboard; PVF, phonemic verbal fluency; PVSAT, Paced Visual Serial Addition Test; RAN, reaction time/motor performance; Raven, Raven's Matrices; RAVLT, Rey auditory verbal learning test; RCF, Rey complex figure; RMT, Recognition Memory Test; RNG, random number generation; SCOLP, Speed and Capacity of Language Processing test; SCWT, Stroop Colour-Word Test; SDMT, Simple Digit Modalities Test; SEQ - motor learning task; SL- Spatial Location; SMA, supplementary motor area; SORNS-Self-Ordered Random Number Sequences; SVF- semantic verbal fluency; Tap, Tapping Test; TD, Tactile Denomination; TMA/B, Trail-making A and B; TPT, Toulouse-Pieron Test; TSEQ, trial-and-error-guided motor sequence learning task; TT, Tower of Toronto Test; VFT, Verbal Fluency Test; VR, Visual Reproduction; VWCAL, Visual-Visual Conditional Associative Learning; VSL, visual sequence learning; WAIS-R, Wechsler Adult Intelligence Scale-revised; WAIS-III, Wechsler Adult Intelligence Scale-III; WCST, Wisconsin Card Sorting Test; WFT, word fluency test;

abnormal or reduced REM sleep,^{58–60} and changes in spindle activity.^{58,60,61} In a study of 10 patients with blepharospasm and oromandibular dystonia, impaired sleep efficiency and decreased REM sleep were found, both of which correlated with the severity of dystonia and EMG abnormalities.⁵⁹ In contrast, a larger study of 24 patients with focal or generalized torsion dystonia (14 primary, 10 secondary) showed that sleep architecture and organization did not vary significantly from control patients.⁶²

Much like other nonmotor symptoms in dystonia, the etiology of sleep abnormalities may include primary effects of dystonia on sleep as well as secondary effects of pain and medications. Some of the patients in the aforementioned studies were on benzodiazepines, known to change sleep architecture and spindle activity.⁵⁷ Anticholinergic medications may also account for some of the sleepiness seen in patients with high ESS scores.⁵⁷ There is conflicting evidence about whether the severity of dystonia is associated with the occurrence of sleep disorders. Although impaired sleep efficiency, decreased REM sleep, and sleep quality have all been linked to severity of motor symptoms in focal or cervical dystonia,^{59,63} excessive daytime sleepiness was not correlated with scores on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) or its subscores in another study.⁵⁷ There is evidence that at least certain forms of dystonia, including blepharospasm and Meige's syndrome, may persist during sleep, although its frequency and severity are decreased.⁶⁴ Whether this may affect sleep quality is unknown. Restless legs–like symptoms were found in 6 of 34 patients with DYT5 dystonia prior to the initiation of levodopa in a detailed clinical evaluation.⁶⁵ Finally, Wetterberg (1978) found decreased amplitude of melatonin fluctuations in a patient with “hereditary dystonia”; however, this was not replicable in a larger series of 19 patients.⁶⁶

Sleep impairment and its secondary symptoms are particularly burdensome for patients with dystonia. Studies using the Cervical Dystonia Impact Scale, a rating scale for measuring the health impact of cervical dystonia based on patient perceptions,⁶⁷ have shown that a large percentage of patients with dystonia report sleep affecting their QOL. Subjective ratings of both energy and tiredness are associated with QOL, even when controlling for depression. In fact, the tired subscore of the Visual Analogue Mood Scale was found to be the most strongly correlated with overall QOL in our recent study.⁴

Additional research analyzing polysomnograms in patients off antidystonic medications would help to clarify if changes in sleep structure are a primary or secondary effect in dystonia. Also, studies assessing whether treatment of motor symptoms alone improves objective sleep measures are needed. Finally, although fatigue plays a significant role in QOL in dystonia, no

studies to date have assessed the symptom as a manifestation of dystonia.

Pain (n = 12)

Pain is one of the most common and disabling complaints in many patients with dystonia. Studies suggest that the prevalence of pain in patients with cervical dystonia ranges from 67% to 75%.^{68–70} In cervical dystonia, pain is often experienced in the head and neck and down the ipsilateral arm on the side to which the head is rotated.⁶⁹ The sternocleidomastoid and trapezius are the most frequently involved muscles.⁷¹ Although it may seem obvious that dystonic muscles would be painful, not all patients with similar degrees of dystonia report equal amounts of pain. Although degree of head deviation and subjective muscle tension may correlate with pain level, somewhat surprisingly, the objective severity of neurologic signs has not.⁶⁹

One potential reason that pain is so prevalent in dystonia is that the threshold for experiencing pain may be reduced. In a small study of 9 patients with idiopathic cervical dystonia, pain-pressure thresholds were about 2 times lower in the dystonia group versus a group of age- and sex-matched controls.⁷² Patients with dystonia may also have alterations in pain processing, even in body parts without dystonic involvement. For example, in the same study, the nonaffected masseter muscles of patients with idiopathic cervical dystonia also showed reduced pain-pressure thresholds compared with the control group.⁷² Another potential mechanism for excessive pain includes alterations in the somatosensory system that have been documented in patients with focal or generalized dystonia. These include changes in excitability on neurophysiological testing, abnormal representation in S1 of dystonic body parts, and changes in somatosensory cortical activity during movement.⁷³ Ongoing depression, common in this population, correlates with symptoms of pain. Last, sleep itself may mitigate against pain, as cervical spinal pain intensity and unpleasantness were reduced by about 50% overnight in 1 study of patients with idiopathic cervical dystonia.⁷⁴

To our knowledge, no recent studies have evaluated any other pharmacologic agents to specifically treat either primary or secondary dystonic pain symptoms. Double-blind, randomized controlled trials assessing whether analgesic agents could lead to objective measures of additional decreased pain in dystonia patients are needed, particularly in patients refractory to botulinum toxin. Whether the type and location of dystonia correlate with pain level is also not known.

Autonomic Symptoms (n = 2)

Patients receiving botulinum toxin, especially type B, may experience autonomic symptoms including dry

mouth, blurred vision, reduced sweating, constipation, and urinary retention.⁷⁵ Anticholinergic medications may also cause similar symptoms. Autonomic symptoms have rarely been reported outside the context of these medical treatments or secondary dystonia (complex regional pain syndrome and brain injury). Tiple et al (2008) found that patients with cervical dystonia had mild subclinical changes in some measures of heart rate variability and baroreflex sensitivity that were present before receiving botulinum toxin injections.⁷⁶ Aside from this, no reports of erectile, sexual, urinary, or bowel dysfunction were found. Future research should attempt to further clarify whether autonomic symptoms are seen outside known side effects of treatment.

Conclusions

In addition to there being the more visually apparent and well-defined motor symptoms of dystonia, there is emerging evidence for the presence of nonmotor symptoms in primary and other genetic forms of dystonia. The available evidence can at times be conflicting, and the question remains: are these nonmotor symptoms secondary to motor causes and medications, or do they reflect a primary defect in neuronal processing or neurochemistry? Given that nonaffected family members with dystonia biomarkers can be affected and that symptoms can be seen prior to the onset of motor symptoms, it seems likely that the primary effects of the disease are at least partly to blame. Although the pathophysiology and neuroanatomy of these effects have not been clearly elucidated, the underlying defects in dystonia may provide a substrate for nonmotor symptoms to develop, particularly when combined with motor features of the disease and/or side effects of treatment.

Further studies are clearly indicated. First, by investigating the specific cortical and subcortical networks involved in dystonia, the genesis of the disease and the development of nonmotor symptoms might be better understood. Defining the neuroanatomy and pathways involved in these symptoms by using functional imaging studies may yield new treatment strategies. Using such studies to image nonmanifesting carriers of dystonia genes may shed light on a “pre-motor” phase of dystonia, akin to what is described in PD. We also recommend a formal presurgical psychiatric evaluation for DBS candidates to screen specifically for mood disorders, given their prevalence in dystonia. This should include an assessment from a psychiatrist as well as a standardized measure of depression. Development of carefully designed prevalence studies of all nonmotor symptoms, controlling for secondary effects of motor symptoms and side effects of medicine, are needed.

Much has been learned about the manifestations of dystonia including both motor and nonmotor symptoms over the past 2 decades. We must understand that nonmotor manifestations will likely widely vary among dystonia subtypes. Only when the entire phenotype of dystonia is fully understood will we be able to provide appropriate, comprehensive care and measurable improvements in QOL for these patients. ■

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