

Non-Motor Symptoms in Cervical Dystonia: A Review

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Abstract

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements, postures, or both. Dystonic movements are typically patterned, associated with twisting of body parts, and may have tremulousness. Dystonia is usually initiated or worsened by voluntary action and associated with overflow muscle activation. Cervical dystonia (CD) is the most prevalent form of dystonia. CD is a condition characterized by cranial muscle overactivity leading to abnormal intermittent or continuous posturing of the head. Non-motor symptoms are comorbidity of dystonia, which significantly hampers the quality of life among these patients. The symptoms can be as a result of the dystonia itself. However, studies have highlighted the involvement of cortical-striatal-thalamocortical circuits in primary dystonia that could be the pathophysiological basis for the non-motor symptoms. The non-motor symptoms that are commonly associated with dystonia are anxiety, depression, restless leg syndrome, excessive daytime sleepiness, cognitive disturbances, and poor sleep. This review attempts to summarize the literature on non-motor symptoms in patients with CD.

Keywords: Anxiety, cervical dystonia, depression, non-motor, sleep

INTRODUCTION

Cervical dystonia (CD) is the most prevalent form of dystonia.^[1,2] It is a condition characterized by cranial muscle overactivity leading to abnormal intermittent or continuous posturing of the head.^[1,3] The activation of various cervical muscles gives rise to multiple types of neck posturing (retrocollis, anterocollis, torticollis, laterocollis). A combination of these movements has been the most common manifestation of CD with 61-66% of the patients having a combination of actions.^[2,3]

CD has many non-motor symptoms that add to the comorbidity of the disease. Thirty-six percent of the patients reported non-motor symptoms significant enough to cause impairment of activities of daily living. The degree of non-motor symptoms did not correlate with the severity of CD ($r = 0.23$, $P = 0.02$).^[4]

The emotional state has been linked to the dysfunction in the prefrontal cortex. This area has shown altered function and morphology in patients with dystonia and hence could explain mood disturbances in these patients.^[5-7] Anxiety, depression, behavioral and cognitive problems, pain, poor quality of life, employment issues, sexual dysfunction, restless legs syndrome, and excessive daytime sleepiness are common non-motor symptoms that are challenges in patients with CD.

Pathophysiology of non-motor symptoms in dystonia

The role of basal ganglia in the non-motor symptoms has been identified with the recognition of subcortical circuits that connect with the frontal cortex, governing executive function, saccadic eye movements, motor activity, motivation and behavioral aspects. Caudate nucleus, in particular, appears to be involved in cognition. Cortico-striato-thalamo-cortical loop has been implicated in cognitive symptoms in basal ganglia

disease.^[8] Pathology of frontal subcortical circuits is implicated in mood disorders in patients with basal ganglia disorders such as dystonia^[6,9] and parkinson's disease.^[10,11] The modulation of the motor cortex by the sensory input is mediated by striatal neurons.^[8] In patients with dystonia, primary abnormality in sensory input and assimilation has been found to give rise to sensory abnormalities.^[12]

METHODOLOGY

Pubmed search was carried out using keywords such as "cervical dystonia" and "sleep", "non-motor symptoms", "anxiety", "depression", "quality of life", "sexual dysfunction", "cognition" and "memory". Studies that described non-motor symptoms after administration of botulinum toxin were excluded.

Four hundred forty-two studies were found in the category of CD and among them, 61 studies were found relevant for the review [see Figure 1]. In this article, we review the currently available literature on the non-motor symptoms of CD.

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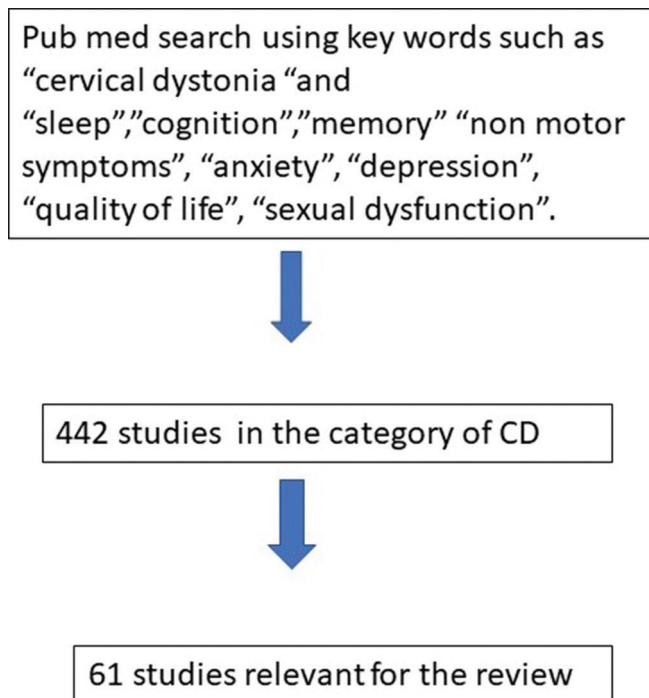


Figure 1: Methodology of selecting the articles

Anxiety and depression

Basal ganglia have a role in emotions, and dystonia and emotional dysregulation could be the result of basal ganglia dysfunction.^[13,14]

Fabrizi *et al.*, in a study of 89 patients with focal dystonia showed that 57.3% of the patients had psychiatric disorders. Mood and anxiety disorders were the most common disorders (21.3%). Adjustment disorders and obsessive-compulsive disorders were seen in 8.9% and 3.3% of the patients, respectively. There was no correlation between the severity of depression and the severity of dystonia. There was no difference in the Hamilton Anxiety Rating Scale (HAM-A) scores between patients with dystonia and controls.^[14]

In a study by Lewis *et al.*, that involved 329 patients with focal, generalized, segmental, and hemidystonic forms of dystonia, among various types of dystonia, the highest incidence of self-reported depression was among individuals with the dystonic posturing of the neck.^[15] Low self-esteem and negativity that prevailed regarding self-image (negative body concept) also possibly contributed to the depression.^[15] The self-esteem scores profoundly influenced depression scores. Self-esteem accounted for 56% of the variance of Beck depression scores. However, the severity of depression was strongly related to the degree of dystonia.^[15]

Among patients with generalized dystonia, focal, segmental, and hemidystonia, patients with generalized dystonia had the least depression scores. A likely explanation for this finding could be the younger age of onset of generalized dystonia, and hence patients get the opportunity to acclimatize themselves to the abnormal posturing.^[15]

In another study by Avanzino *et al.*, mild depression was observed in 15% of the patients, moderate depression in 7%, and severe depression in 2% of patients compared to 2% in controls. Anxiety and depression were significantly more in patients with CD compared to controls.^[16]

Moraru *et al.* reported co-existing psychiatric disorders in 55% of the patients, among which the most common diagnosis was a mixed depression in 37.5% of the patients and anxiety disorder in 40% of the patients.^[17] Among them, 30% of the patients had mild depression, 7.5% of the patients had moderate depression, and 5% showed severe depression. A pre-existing psychiatry disorder before the onset of CD was seen in 42.5% of the patients. Alcohol dependence and somatoform disorders have also been observed in patients with CD. Based on the symptom checklist 90 (SCL-90) index, CD patients with depression have increased levels of psychopathology. There was no correlation between depression and duration of CD.^[17]

However, other studies showed a relation between the duration of CD and depression.^[15,18] No correlation was seen between gender and age of onset of dystonia with depression.^[15]

In a study by Yang *et al.*, depression was found in 20% of the patients with CD, and anxiety was found in 28.3% of patients with CD. Neither anxiety nor depression had any correlation with the severity of the motor function.^[19] Depression correlated positively with sleep impairment.^[19,20]

However, another study by Scheidt *et al.* showed a correlation between depression and laterocollis on Tsui index. In this study, 23% of the patients with CD had depression and 28% of the patients had anxiety.^[21] Depression was self-reported by 63.6% of the patients and anxiety was self-reported by 62.6% of the patients. In another study, 47.5% of the patients with CD reported depression. Botulinum toxin A (Bont A) toxin improved depression.^[22]

Patients with dystonia of upper face reportedly had a lower level of anxiety compared to CD. Patients with laryngeal dystonia also had a higher level of anxiety compared to patients^[21] with dystonia of the upper face.^[23] However, there was a difference in the level of depression among patients with various focal dystonia.

In a study by Gündel *et al.*, in patients with CD, alopecia areata, and the general population, major depression (single episode) was seen in 12.5%; recurrent depression in 6.3%, anxiety disorder in 68.8%, dysthymia in 2.1%, and social phobia in 54.2% of the patients with CD. In the same study, major depressive disorder (single episode) was seen in 17.3%, major depressive disorder (recurrent) in 9.3%, and dysthymia in 5.5% among the general population.^[24]

Among patients with dystonia, quality of life correlated better with anxiety, depression, and fatigue than with the severity of the primary dystonia.^[7] Disturbed mood as evident by Beck

Depression Inventory (BDI) >10, was seen in 25% of patients with CD. BDI and Pittsburgh Sleep Quality Index (PSQI) showed a positive correlation. Severe depression was observed in 8% of the patients with CD.^[25]

Using Minnesota multiphasic personality inventory, 50% of the patients had depression, 32% had anxiety, and 32% had an obsessive-compulsive state.^[26] In yet another study, among patients with CD, 26.4% of the patients were diagnosed with mood disorders, 26.4% of the patients with anxiety, 3% of the patients with obsessive-compulsive disorders, 11.4% patients diagnosed with adjustment disorder, and 64.3% of the patients with CD were diagnosed with psychiatric disorders.^[14] Patients with cervical dystonia also have a higher chance of developing anxiety and depression [Table 1].^[27]

Patients with CD had a higher possibility of developing obsessive-compulsive disorders.^[28] Unlike anxiety and depression that significantly alleviated with Bont A administration, there was no effect of Bont A injection on the severity of obsessive-compulsive symptoms. Obsessive-compulsive disorders were seen more commonly in women (63.5%). Patients with higher Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores had a longer duration of illness and higher scores in the anxiety and depression scales. The most common obsession among these patients was cleanliness, and the most common compulsion was checking. Botulinum toxin injections appeared to lower the degree of anxiety and depression in patients with focal dystonia. The prevalence of obsessive-compulsive disorders in primary focal dystonia ranged between 6.7% and 21.1%.^[28]

Table 1: Studies showing anxiety and depression in cervical dystonia

Author	Year	Country	Sample size	Instrument	Findings
Novaretti <i>et al.</i>	2019	The United States of America	CD (n=28) HC (n=80)	BDI, BAI	Patients have more than twice the risk of developing depression. They have higher chances of developing anxiety.
Antelmi <i>et al.</i>	2017	Portugal	CD (n=20) HC (n=22)	BDI, PSQI	Depression correlated positively with sleep impairment
Yang <i>et al.</i>	2017	China	CD (n=60)	HAMD, HAM-A scores	Depression in 20%, anxiety in 28.3%
Klingelhoefer <i>et al.</i>	2014	United Kingdom	CD (n=102)	Modified NMS quest	Self-reported depression in 30.3% and flat mood in 23.5%
Paus <i>et al.</i>	2011	Germany	CD (n=111)	BDI	Mood disturbances in 25%. Severe depression in 8%
Fabbrini <i>et al.</i>	2010	Italy	CD (n=37)	BDI	Mood disorders in 26.4%. Anxiety in 26.4%
Slawek <i>et al.</i>	2007	Poland	CD (n=101)	Montgomery Asberg Depression rating scale (MADRS)	Depression in 47.5%. No significant correlation between SF 36 and severity of CD. Significant correlation of depression and pain on SF-36
Moraru <i>et al.</i>	2002	Austria	CD (n=40)	BDI	Mild depression- 30%, moderate depression- 7.5%, severe depression- 2%. Duration of clinical symptoms not correlated with depression
Gundel <i>et al.</i>	2003	Germany	CD (n=48) Alopecia areata (n=48)	SCID-structured clinical interview for DSM	Mood disorders - 18.8%, Anxiety disorders- 68.8% among patients with CD. Mood disorders—12.5% anxiety - 33.3% among patients with Alopecia areata
Scheidt <i>et al.</i>	1996	Germany	CD (n=256)	Freiburg questionnaire for dystonia (FQD)	Depression in 23%, anxiety in 28%. Depression correlated significantly with Tsui index and laterocollis
Nickel <i>et al.</i>	1996	Germany	CD (n=256)	FQD	Depression in 63.6%. Anxiety in 62.6%
Eichenseer <i>et al.</i>	2013	United States of America	CD (n=54)	BDI, HAM-A	Mild depression-15%, moderate depression-7%, severe depression-2% anxiety-9% among patients compared to mild depression- 2% in controls, anxiety 2% in controls
Jahanshahi <i>et al.</i>	1990	United Kingdom	CD (n=85) Cervical spondylosis (n=49)	BDI	Higher disability in CD group due to decreased leisure and social activity. Depression is significantly more common in patients with CD. Mean BDI score in CD was 13.4 (SD 9.9)
Duane DD <i>et al.</i>	2011	United States of America	CD (n=108)	MMPI	Depression in 50%. Anxiety in 32%

CD- cervical dystonia, HC- healthy controls, HAM-A- Hamilton anxiety questionnaire, BDI- Beck Depression Inventory, SCID-structured clinical interview for DSM, FQD- Freiburg questionnaire for dystonia, MMPI- Minnesota multiphasic personality inventory

Pain

Pain associated with repetitive posturing of the neck in CD further adds to the disability among patients with CD.^[29] Employment is dismal when pain is associated with neck movements.^[29] Pain is reported to affect 67–75% of individuals with CD [Table 2].^[30,31] Anxiety, fatigue, and pain were other causes that contribute to the disability in CD.^[32] Neck pain improved with sleep. In another study, sleep benefit was also reported concerning neck pain.^[20,31] Neck pain was a major determinant of depression, and impaired quality of life and its alleviation could improve the quality of life in these patients.^[33]

Excessive daytime sleepiness

The excessive daytime sleepiness was higher among patients taking anticholinergics but was the same in patients taking benzodiazepines compared to those patients who were not on any medication.^[34] In one study, excessive daytime sleepiness was found in 20% of patients with CD.^[19] In another study, excessive daytime sleepiness was reported by 5% of patients with CD [Table 3]. In a few other studies, the excessive daytime sleepiness scores of patients with CD were not greater than that of the controls.^[20,35]

There was no correlation between the excessive daytime sleepiness and the severity of CD.^[34] Various theories have

been laid forward to explain the cause of the excessive daytime sleepiness among patients with CD. Some of these are impaired sleep at night and persistent neck muscle activity in sleep.^[36] Daytime sleepiness showed a positive correlation with depression.^[25]

Restless leg syndrome

Restless leg syndrome (RLS) was seen in 18% of patients with CD. In this study, RLS was found to be more common among women. Dopaminergic deficiency may underpin the relation between dystonia and RLS although further studies are warranted.^[25] RLS is also grossly underdiagnosed in this group of patients.

Sleep

Many movement disorders are associated with sleep disturbances.^[37] Sleep disturbances have been reported both subjectively as well on objective measures. In a study by Klingelhofer *et al.*, sleep disturbances were reported by 59.8% of the patients. The sleep disturbances that were reported by the patients were difficulty in sleep initiation and maintenance as well as lack of feeling refreshed after awakening.^[4] More reduced sleep efficiency was reported in patients with CD [Table 4].^[20]

Table 2: Major studies describing pain in cervical dystonia

Author	Year	Country	Sample size	Findings
Novaretti <i>et al.</i>	2019	United States Of America	CD (n=28) HC (n=80)	Compared to controls, patients have five times higher chance of developing pain
Kutvonen O <i>et al.</i>	1997	Finland	CD (n=39) HC (n=18)	Continuous or intermittent pain in 66.6%
Chan <i>et al.</i>	1991	United States of America	CD (n=266)	Pain in 75%
Lobezzo F <i>et al.</i>	1996	Canada	CD (n=9), HC (n=5), pain pressure thresholds were determined	Pain pressure threshold was two times lower than that of controls
Antelmi <i>et al.</i>	2017	Portugal	CD (n=20) HC (n=22)	Pain markedly benefits with sleep
Molho <i>et al.</i>	2009	United States of America	CD (n=155)	Pain correlated with the decreased working capacity

CD- cervical dystonia, HC- healthy controls

Table 3: Comparison of excessive daytime sleepiness in cervical dystonia

Author	Year	Country	Sample size	Instrument	Findings
Smit <i>et al.</i>	2017	Netherlands	CD (n=44) Controls (n=43)	ESS	EDS in 43.2% patients
Yang <i>et al.</i>	2017	China	CD (n=60)	ESS	EDS in 20%
Paus <i>et al.</i>	2011	Germany	CD (n=111)	ESS	EDS-- 5%
Eichenseer <i>et al.</i>	2013	United States of America	CD (n=54)	ESS	No significant difference between EDS and controls
Avanzino <i>et al.</i>	2010	Italy	CD (n=46)	ESS	EDS-8.7%
Trotti <i>et al.</i>	2009	United States of America	CD (n=43) Other movement disorders (n=19) HC (n=49)	ESS	EDS=21%
Antelmi <i>et al.</i>	2017	Portugal	CD (n=20) HC (n=22)	ESS	ESS=3.5

CD- cervical dystonia, HC- healthy controls, ESS-Epworth Sleepiness Scale, EDS-Excessive daytime somnolence

Based on PSQI, poor sleep efficiency was found in 72% of patients with CD.^[20] In another study, impaired sleep was observed in 65% of patients with CD compared to 31% seen in controls.^[35] This difference persisted even after adjusting anxiety and depression.

Patients did not discern a relationship between dystonia and poor sleep.^[25] Depression correlated positively with sleep impairment.^[19,20] No correlation was found between poor sleep quality, with age of onset or duration of symptoms, and the severity.^[25] A significant correlation found between the severity of CD and the PSQI score was lost when adjusted for the BDI score.^[16] In patients with CD, PSQI scores correlated with the duration of the symptoms.^[16] Excessive daytime somnolence was not associated with poorer sleep efficiency in patients with CD.^[20,38] PSQI correlated negatively with sleep efficiency

and positively with sleep latency.^[20] Depression could be the etiological factor resulting in impaired sleep in patients with CD. Sleep impairment could be a co-existing illness with CD.^[16]

Improvement of the dystonia with botulinum toxin did not alleviate sleep impairment or daytime somnolence.^[20,25,35] This indicates that there are intrinsic factors that impair sleep in CD. This hypothesis is further reaffirmed by the fact that patients with dystonia with no neck activity and pain, also reported sleep disturbances.^[16,25]

Polysomnography

Polysomnography studies revealed sleep abnormalities in patients with CD and generalized dystonia. Patients with CD showed poor sleep efficiency, decreased amount of rapid eye movement (REM) sleep, prolonged latency of REM sleep.^[39]

Table 4: Comparison of sleep impairment in cervical dystonia

Author	Year	Country	Sample size	Instrument	Findings
Smit <i>et al.</i>	2017	Netherlands	CD (n=44) HC (n=43)	PSQI	Poor sleepers- 77.3% among patients. PSQI scores were influenced by the severity of cervical dystonia.
Novaretti <i>et al.</i>	2019	The United States of America	CD (n=28) HC (n=80)	PSQI	Higher PSQI scores in patients compared to controls. The quality of sleep was influenced by anxiety and depression scores
Yang <i>et al.</i>	2017	China	CD (n=60)	PSQI	Poor sleepers-71.7%
Klingelhoefer <i>et al.</i>	2014	UK	CD (n=102)	Modified NMS quest	Self reported poor sleep in 59.8%
Paus <i>et al.</i>	2011	Germany	CD (n=111)	PSQI	Poor sleepers- 44%
Avanzino <i>et al.</i>	2010	Italy	CD (n=52)	PSQI	Poor sleep - 72%
Eichenseer <i>et al.</i>	2013	United States of America	CD (n=54)	PSQI	Poor sleep- 65%
Antelmi <i>et al.</i>	2017	Portugal	CD (n=20) HC (n=22)	PSQI	PSQI 6.8±5.6

CD- cervical dystonia, HC-healthy controls

Table 5: Polysomnography studies in Cervical Dystonias

Author	Sample size	PSG	Results
Lobbezoo 1996	9 patients with cervical dystonia, medication was discontinued one week prior to PSG	2 nights of PSG, EMG electrodes placed on trapezius and sternocleidomastoid	Increased sleep latency, cervical EMG activity decreases to normal state from wakefulness to N2
Fish <i>et al.</i> 1990	14 patients with primary generalized dystonia, 10 patients with secondary dystonia, 39 patients with other neurological disease, 10 normal controls	1 night of PSG recording after 1 night of adaptation in the laboratory	Only one patient had sleep spindles that were abnormal in duration and amplitude.
Jankel <i>et al.</i> (1984)	9 patients with torsion dystonia and 9 age and sex-matched controls	3 nights of recording	Most severely affected patients had poorest sleep efficiency, greater latency to sleep onset, decreased REM sleep, high amplitude sleep spindles, greater number of awakenings
Jankel <i>et al.</i> (1983)	4 patients with generalized dystonia on varying combinations of trihexylphenidyl, diazepam, chloral hydrate, dantrolene. Age and sex-matched controls	3 nights of polysomnography	Greater amplitude of sleep spindles compared to controls. Poor sleep efficiency, increased awakenings, decreased total sleep time, increased sleep latency, decreased REM sleep.
Antelmi <i>et al.</i> 2017	22 patients with isolated cervical dystonia and 20 healthy controls	1 night of PSG	Sleep efficiency, sleep latency is significantly increased in patients with cervical dystonia. Muscle activity progressively decreases as the sleep deepens

PSG- Polysomnogram, EMG- Electromyogram, EEG- Electroencephalogram, REM- Rapid eye movement, WASO- Wake after sleep onset

Transient cervical muscle activity presenting as bursts have been observed during REM sleep.^[36]

Poor sleep efficiency was reported in patients with CD. Polysomnography studies also reported that these patients had increased sleep latency and REM Latency.^[20] But another study showed that apart from a variable sleep latency, sleep architecture remained unfazed in patients with CD.^[40] Increased latency to sleep has also been observed in patients with primary generalized dystonia.^[41] The activity of the dystonic muscles significantly decreased as the patient progressed towards deeper stages of sleep.^[20]

Sforza *et al.* reported sleep impairment, decreased slow-wave sleep, decreased REM sleep, and increased arousals.^[42]

Higher PSQI scores correlated with low sleep efficiency and increased sleep latency. There was no correlation between sleep architecture and the duration and severity of the illness.^[20]

Patients with generalized dystonia have poor sleep latency, frequent night-time awakenings, and decreased REM period. Interestingly high amplitude sleep spindles (amplitude between 50–100 μ v) with no change in the frequency were observed.^[43] In another polysomnographic study on generalized dystonia, the high amplitude spindles were seen in a patient with the most severe form of the disorder.^[41] Studies by Wein *et al.* in patients with primary and secondary dystonia revealed unusually large spindles that had occasionally turned hypersynchronous. The large

Table 6: Major studies showing employment status in patients with cervical dystonia

Author	Year	Country	Sample size	Findings
Martikainen <i>et al.</i>	2010	Finland	CD (n=247)	Premature termination of job 10 years earlier
Comella and Bhatia	2015	United Kingdom	CD (n=1071)	Twenty six percent of CD was unable to work
Nickel <i>et al.</i>	1996	Germany	CD (n=256)	Sick leave during the study-14.4% Severe disability at the workplace- 51% Disability at home- 64.4%
Scheidt <i>et al.</i>	1996	Germany	CD (n=256)	Premature retirement- 23%
Skogsied <i>et al.</i>	2005	Norway	CD (n=62)	Employment rate dropped from 84% at the onset of cervical dystonia to 47% at the time of botulinum toxin initiation
Molho <i>et al.</i>	2009	USA	CD (n=155)	Loss of job=18.3% Decreased productivity-68.9%

CD- cervical dystonia

Table 7: Major studies describing the quality of life in cervical dystonia

Author	Year	Country	Sample size	Instrument	Findings
Smit <i>et al.</i>	2017	Netherlands	CD (n=40)	RAND-36, NMS questionnaire	95% of patients reported atleast one non motor symptoms. fatigue and poor sleep quality were the most important contributors to the poor quality of life
Slawek <i>et al.</i>	2007	France, Poland	CD (n=101)	SF-36	Quality of life poorer in women. Disease duration does not affect the quality of life. Financial status affects general health perception
Ben Shlomo <i>et al.</i>	2002	United Kingdom	CD (n=289)	SF-36	Inability to accept illness, decreased socialization was associated with poor quality of life. Age, sex did not affect the quality of life. Longer duration of illness was associated with better quality of life. Depression and anxiety the most important predictor of poor quality of life.
Page <i>et al.</i>	2007	United Kingdom	Generalized, focal segmental dystonia (n=276)	SF-36, European quality of life questionnaire	Patients with dystonia had worse quality of life. Quality of life worse in focal dystonia than generalized dystonia. Employment status, severity of dystonia affected the quality of life
Camfield, Ben Shlomo <i>et al.</i>	2002	United States of America	CD (n=289)	SF-36	Quality of life worsens as the age progresses. Lower education status is associated with worse quality of life. SF 36 scores are worse among women
Soeder <i>et al.</i>	2009	United States of America	Primary dystonia (n=77)	SF-36	Anxiety, depression, and tiredness are determinants of poor quality of life
Pekmezovic <i>et al.</i>	2008	Serbia	Focal dystonia (n=157)	SF-36, HAM-A, HAMD	Poor quality of life in patients with dystonia. Anxiety, depression correlated with SF36 scores in patients with cervical dystonia and blepharospasm. Pain correlated with depression

CD- cervical dystonia, RAND 36- SF 36- short form health survey, HAM-A- Hamilton Anxiety Questionnaire, HAMD- Hamilton depression Questionnaire, NMS- nonmotor symptom questionnaire

spindles were more frequently encountered in patients with generalized dystonia. The sleep onset latency was increased, REM latency was high, and REM duration was low. However, the details of the medication were unavailable in the study.^[44] Patients also showed similar polysomnography findings of a greater number of nighttime awakenings, decreased the duration of REM sleep, and increased sleep latency.^[41] A possibility of large spindles being related to the disease process was contemplated upon.^[41] The overactivity of the serotonergic raphe due to damage to locus coeruleus might lead to disinhibition of non-rapid eye movement (NREM) sleep leading to high amplitude of spindles.^[43] However, in another study, sleep spindles abnormalities were seldom found (found in 4 out of 24 patients with torsion dystonia). In this study of patients with primary and secondary dystonia, only 1 out of 24 patients had abnormal spindle morphology. The authors hence concluded that spindle production is normal in dystonia [Table 5].^[45]

Cervical muscle activity reduced in patients with CD during the transition from wakefulness to stage 2. Also, cervical muscle activity decreased in the supine position.^[46] The contractions of the muscles among patients with CD fell lower than that seen among controls during sleep.^[20] A possible explanation might be the need for more significant rest required by the neck muscles that are overexerting, hence maintaining homeostasis with sleep acting as an adjunct.^[20,27] Specific theories have been postulated—gamma-aminobutyric acid (GABA) induced inhibition during sleep, possible basal ganglia disconnection from the cortex.^[20]

Cognition

Aberration in subcortical circuits connecting basal ganglia and frontal regions such as the dorsolateral prefrontal cortex, cingulate, and orbitofrontal cortex accounts for cognitive dysfunction in disorders of basal ganglia.^[8] Deficits in attention and executive function have been noted among patients with primary dystonia.^[47] Patients with CD have been found to have cognitive deficits such as impaired set-shifting, impaired working memory, and defective visuomotor ability.^[48] However, another study comparing visuospatial function in patients with CD and controls showed no difference between patients and controls.^[49] In another study, patients with CD were reported to have impairment in the analysis of the theory of mind, suggesting deficits in social cognition.^[50] The presence of pain that affects attention, presence of coexisting mood disorder, and drugs like anticholinergics and benzodiazepines also accounted for cognitive deficits in these patients.^[51]

Employment

The age of onset of CD is around 41 years, during which time individuals are generally employed.^[31,52] The distressing symptoms in patients with CD compel them to forsake jobs prematurely, by at least 10 years.^[53]

Employment issues in CD have been addressed by many studies.^[54-56] Twenty-six percent of the patients with CD were unable to work or disabled due to the illness.^[57] In another

study, Nickel *et al.* described the employment in patients and reported 14.4% of the patients were on sick leave during the study. Fifty-one percent of the patients reported severe impairment in activities at the workplace. Disability in performing household chores was reported by 64.4% of the patients and impairment in walking was reported in 55.3% of the patients.^[55] Fifty-nine percent of the patients with CD reported difficulty in driving car.^[55] Decreased participation in social events was found in 65% of the patients with CD. Women reported more impairment in activities of daily living compared to men. Early retirement was seen in 23% of the patients due to illness [Table 6].^[21]

In another study by Molho *et al.*, 53.3% of the patients reported impairment of responsibilities at the workplace, including 18.9% of patients who lost their jobs. Decreased productivity was reported by 68.9% of patients. The employment status correlated with neck pain, but not with the severity of CD.^[29] The rate of employment drastically dropped to 47% by the time of initiation of botulinum injection. The evaluation for the employment status following long-term botulinum injection revealed a significant reduction in the number of non-employed patients. Two-thirds of the patients who were on sick leave at the initiation of treatment resumed work following long-term botulinum injection.^[54]

Quality of Life

Various factors have been observed to affect the quality of life among patients with CD.^[58-60] Some of these are pain, health perception, physical and mental health impairment resulting in limitation of their role at work and family. Women with CD were prone to even more impaired social functioning as evidenced by lower SF-36 scores.^[22] Financial status appeared to affect the way patients with CD perceived their general health. Disease duration had no impact on the quality of life.^[22] Inability to accept the illness, a higher degree of perceived stigma, and decreased socialization were associated with poorer quality of life [Table 7].^[22]

However, in another study by Ben-Shlomo *et al.*, age or level of education did not influence health-related quality of life. The severity of the disease, as well as reduced self-esteem, further contributed to the mental health component of the quality of life. Individuals with longer duration of the disease had better quality of life, which could be due to a longer time to adapt to the illness.^[56]

The perception of the illness and the coping strategies undertaken to deal with the disease appeared to be the most critical factors influencing the quality of life when compared to disease duration, anxiety, social support, depression, and educational background.^[56] Another study by the same workers showed that, in the field of general health, quality of life also worsens as the age of the patient increases, not affecting the other fields of quality of life. The score was better among males compared to women and in patients with a higher educational background. When the quality of life of patients

with Parkinson's disease, multiple sclerosis, and stroke was compared with that of CD, patients with CD fared worst in the emotional aspects. Impaired physical role in CD could result from pain and avoidance of activities that make the dystonic posturing apparent.^[57]

Patients with dystonia have impaired quality of life, which is significantly associated with tiredness. Anxiety, depression, and subjective confusion were also determinants of the poor quality of life. The emotional state is linked to the prefrontal cortex. This area has shown altered function and morphology in patients with dystonia and hence could explain mood disturbances in these patients.^[5,7,61]

Quality of life appears to be most affected by depression.^[22] In a study by Ben Shlomo *et al.*, anxiety, as well as depression, contributed the maximum to the quality of life.^[56]

The benefit of patient societies was reported by 86% of the patients. Following the medical intervention, 64% of patients with CD reported improvement in their symptoms. Among patients with CD receiving Botulinum A (Bont A) toxin, 62% of the patients reported improvement, 25% of the patients reported non-improvement, and 13% of the patients reported worsening of the symptoms.^[62]

Patients with CD felt stigmatized with their physical appearance due to the twisting movement. Despite the improvement in symptoms with Bont A injections, quality of life failed to improve significantly in patients with CD. The transient benefit with botulinum toxin could be the possible cause of the lack of significant improvement.^[33]

Among patients with dystonia, quality of life correlated better with anxiety, depression, fatigue than with the severity of the primary dystonia.^[7]

Sexual dysfunction

Perozzo *et al.* evaluated sexual well being in their cohort of 30 patients of spasmodic torticollis by using the Sexual Functioning Inventory (SFI), a reduced form of the Golombok Rust Inventory, previously employed in patients with Parkinson's disease along with measures of depression and anxiety. The SFI is a 15-item self-rating scale evaluating seven types of sexual disorders: infrequency, non-communication, dissatisfaction, avoidance, non-sensuality, premature ejaculation-vaginismus, and impotence-anorgasmia. Men and women were given two different forms of the questionnaire. The higher score indicates higher sexual dysfunction (min score is 15; maximum is 60). They found that dystonic patients demonstrated high sexual dysfunction. The quality of sexual life in females was poorer as compared to males. Central basal dysfunction was proposed as the mechanism for this dysfunction.^[63] Marek *et al.* investigated 65 patients of CD with Arizona Sexual Experience Scale, a validated self-rating scale. Sexual dysfunction was present in 29 (45%) CD patients, as compared to the control sample (n = 14, 24%, $P = 0.009$). The predictors were age of onset of dystonia, duration, and severity as assessed by Tsui index.^[64]

SUMMARY

The non-motor symptoms are an important cause of morbidity in patients with CD. Impairment of sleep, poor quality of life with the loss of productive employment, excessive daytime sleepiness with psychiatric comorbidity are interrelated and are a cause of major concern in these patients. Cognition is subclinically impaired but more studies will highlight if cognitive disturbances are indirectly leading to psychiatry symptoms and vice versa. Knowledge of these non-motor symptoms, identification and timely management can have a significant impact on the management of patients suffering from CD.

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Conflicts of interest

There are no conflicts of interest.

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