Chapter 3

Non-Motor Symptoms in Patients with Primary Dystonia

Nikolina I. Semerdjieva and Ivan G. Milanov

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Abstract

Isolated dystonia, previously referred to as primary, is the third most common movement disorder, characterized by involuntary muscle contractions causing abnormal movements and postures with or without the presence of tremor. No matter monogenic or sporadic, the form of dystonia is a growing evidence, suggesting the presence of non-motor components to the disorder. Dystonia patients suffer from reduced quality of life, which might be related not only to the dystonic movements itself but to different non-motor symptoms and signs, as well. Based on literature review, this chapter aims to focus on the association of different types of isolated/primary dystonia (forms of focal, segmental, and generalized dystonia) with some non-motor disorders, including sleep and psychiatric disorders, cognition, as though as pain and sensory symptoms, their pathophysiological and biochemical mechanisms, relations with the symptomatic treating strategies for the abnormal movements, and specific treatment for the non-motor signs.

Keywords: dystonia, non-motor, mechanism, quality of life, treatment

1. Introduction

The concept of dystonia has been changing much over time. Nowadays, dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation [1–3].

In 2013, an international panel of experts provided a consensus update on definition, phenomenology, and classification of dystonia [4–6]. Previously, dystonia syndromes were classified upon etiology, age at onset, and body distribution [4]. Dystonia was referred as primary where the dystonia with or without the presence of tremor was the only symptom present, frequently inherited as monogenic traits and usually lacks gross neuropathological changes [4, 5]. Dystonia-plus syndromes encompassed disorders where dystonia was a prominent feature, but combined with other neurological abnormalities (myoclonus, parkinsonism). In the heredo-degenerative form, dystonia was a symptom of an underlying neurodegenerative disorder, and secondary dystonia included a heterogeneous group of conditions, induced by structural lesions, infections, metabolic, or systemic disorders [6].

The present classification is based on two, more refined axes, namely clinical characteristics and etiology. The first encompasses age at onset, body distribution, temporal pattern, coexistence of other movement disorders, and other neurological manifestations. The body distribution is described as focal, segmental, multifocal, generalized (with or without leg involvement), or hemidystonia. Associated features distinguish isolated dystonia in both genetic or idiopathic cases that are often resembled to as primary dystonia, and combined (dystonia plus, heredo-degenerative, secondary) dystonia. The second axis allows further division according to the presumed etiology [2–6].

Although dystonia is a rare condition in general population, the "pure," primary, isolated dystonia is the third most common movement disorder, after essential tremor and Parkinson's disease [7], and besides, the disorder influenced a major impact on the quality of life [1, 7].

Concepts on phenomenology has also renewed with decades, considering dystonia to be a solely motor disorder to an increasing recognition of associated neurological or psychiatric features which indicate that the disorder is not purely motor [2]. This resembles the growing knowledge on dystonia's pathophysiology where the recent insights from neurophysiologic studies identified functional abnormalities in the basal ganglia sensorimotor network and, more recently, the cerebello-thalamo-cortical pathway [7]. Besides the well-known lack of inhibition at different nervous system levels, dystonia is specifically characterized by abnormal sensory feedback, maladaptive plasticity in the sensorimotor cortex, and loss of cortical surround inhibition [4, 7].

Bearing in mind the new classification, where the term "primary" is no more recommended, and the circumstance that in majority of cases it resembles the new and more precise term "isolated", both terms are used in this chapter, in order to be correct when providing information from the studies cited, fully understanding that some time and efforts are needed to completely replace the old terminology with the new one.

Based on literature review, this chapter aims to focus on the association of different types of primary/isolated (forms of focal, segmental, and generalized) dystonia with some non-motor disorders, including sleep and psychiatric disorders, cognition, as though as pain and sensory symptoms, their pathophysiological and biochemical mechanisms, relations with the symptomatic treating strategies for the abnormal movements, and specific treatment for the non-motor signs.

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2. Psychiatric disorders

Comorbid psychiatric disorders are defined as arising due to the effects of the movement disorder, but not merely present by coincidence. The existing epidemiological data demonstrate a 3–6 fold increased prevalence of psychopathology in dystonia patients compared with that in the general population [8]. Some studies reported more frequent psychiatric problems even in populations with different chronic disorders, suggesting that they may be a primary feature of the disorder [9, 10]; however, other did not confirm that observation.

The lifetime prevalence of psychiatric disorders can reach up from 70.9% in cervical dystonia (CD) and blepharospasm (BS) patients [10] to 91.4% in CD patients, compared to 35% in the general population [9–11]. Compared to CD and BS, data are limited on the prevalence of psychiatric disturbances with other forms of dystonia. Laryngeal dystonia is associated with an increased point prevalence but not lifetime risk of psychiatric comorbidity as compared to patients with vocal cord paralysis [12]. Another study failed to find differences in the point prevalence of psychiatric diagnosis in patients with laryngeal dystonia as compared to healthy age-matched controls [13]. Patients with focal hand dystonia did not show a difference in rates of primary psychiatric diagnoses, as compared to healthy controls [13], but in musician's dystonia, increased anxiety symptoms were reported compared to unaffected musician controls [14].

Behavioral and mood disorders have been studied most thoroughly in dystonia [15]. Depression and anxiety disorders were reported to be most frequent in isolated focal or segmental dystonia, with some studies reporting a higher prevalence of depression [13, 16, 17], and other of anxiety symptoms/panic disorders (29.5%), social phobia (41.3%) [9, 18], obsessive–compulsive symptoms (6.8–19.7%) [8, 9, 18–20], or alcohol abuse [9, 21, 22]. Psychiatric disorders, such as drug and substances abuse, psychotic episodes or schizophrenia, are occasionally reported in dystonia patients, with much less frequency [23, 24].

Studies of frequency and type of psychiatric disorders in patients with isolated focal dystonia have some limitations due to methodological differences in both the diagnostic criteria and the psychiatric interviews used, as some studies use the DSM criteria and others use questionnaires, which might lead to variations in the rate of psychiatric comorbidity [25]. The limited data and varied prevalence for psychiatric illnesses across different types of dystonia may confound interpretations of the etiology of psychiatric disorders as well [11, 26]. There may also be recall bias in studies of lifetime prevalence [11]. Notwithstanding these limitations, the majority of clinical investigations indicate psychiatric disorders to be frequently encountered in isolated/primary dystonia.

2.1. Depression

2.1.1. Epidemiological and etiological basis

Depression, along with the anxiety spectrum, is the most reported psychiatric disorder in the primary/isolated dystonia population. Depression is highly reported in CD patients, most

often in the diapason from 25 [26, 27] to 47% [28, 29], and that might be due to the fact that this is the most frequent form of isolated dystonia. Lifetime and point prevalence of major depression are increased. The lifetime risk for CD patients meeting diagnostic criteria for depression ranges from 15 to 53.4% [11]. A high prevalence of depression has also been observed in BS, ranging from 15 [26] to 37% [30]. Although increased, as compared to general population, some studies revealed that depression in BS did not statistically differ from those in patients with hemifacial spasm (HFS) [13, 31]. Some data suggested an increased depression level in laryngeal and focal hand dystonia, compared with healthy controls [8]. The lifetime prevalence of major depression in primary focal hand dystonia was reported to be 25.6%, and the recurrent major depression—17.95%. There is also more commonly a family history of depression in focal hand dystonia than in controls (41.02%). These rates contrasted with the lifetime prevalence of major depression in the general population of 17% [18]. Depression is reported at high level in axial dystonia (33%) [8], as well as in non-focal (e.g., segmental and generalized) and genetic forms of dystonia [32]. In manifesting and non-manifesting DYT1 mutation carriers, the risk of recurrent major depressive disorder is increased compared with non-carriers. Carriers had earlier age at the onset of a recurrent major depressive disorder than non-carriers, and the severity of motor signs was not associated with the likelihood of recurrent depression [33, 34]. By contrast, depression in isolated focal dystonias is estimated to be less frequent when compared to Parkinson's disease, which might be explained by the different underlying pathophysiological mechanisms [23].

There is conflicting epidemiological evidence as to whether depression is secondary to motor manifestations and subsequent psychosocial impairment, or a primary feature of the disease [25]. Factors in the etiology of depression are believed to be adverse life events and dysregulation of monoamine and dopaminergic neurotransmitter metabolism, with genetic predisposition playing a role [8]. It is proposed that cognitive and neurochemical abnormalities trigger aberrant activity within the basal ganglia which contributes to the clinical features of depression [8]. Adverse life events involving loss, identified as specific precipitants of depression, are prominent in dystonic patients. Depression in dystonia can be triggered by lack of satisfaction with social support, maladaptive coping strategies, self-depreciation, and altered body concept [8, 32, 35]. The disability and pain induced by the motor disorder may act as a nonspecific stressor and combine with other factors to induce depression [8]. It seemed that some proportion of depression may be secondary to motor disability and pain, as improvement in mood is reported in several studies with successful treatment of dystonia [15, 23].

The theory of deranging monoamine metabolism in dystonic patients may play a role. For example, a decreased synthesis of monoamine neurotransmitters in patients with DYT 5 dystonia may also have higher rates of depression than in the general population, perhaps due to a reduced conversion of tryptophan to serotonin [15]. Although there is no evidence from human studies, researches of a hamster model of primary dystonia have demonstrated altered levels of 5-hydroxytryptamine and noradrenaline in the basal ganglia, suggesting that monoamine metabolism may be abnormal in human primary dystonia, potentially predisposing to depression [8].

Often, depression manifests before the onset of the movement disorder, thus not representing a mere reaction to its burden [23]. A number of studies reported a higher pre-morbid incidence of depression and anxiety [9, 10, 16, 17, 20, 21, 23, 36] as well. The manifestation of depressive

symptoms preceding the onset of dystonia symptoms may lead to the hypothesis that depression forms part of the phenotype of isolated, especially focal, dystonia [21]. Although some effect on botulinum toxin (BoNT) treatment upon depression severity in CD patients was reported [30, 37], suggesting secondary depression, no similar association was observed in BS patients [30]. Moreover, an independent course of depression and dystonia was presented [26] in CD patients followed up for a period of 5 years. CD patients were BoNT treated, and the severity of dystonia was milder at the end of the follow-up, whereas no differences were observed in the severity of psychiatric symptoms. Psychiatric disorders remaining stable in spite of an improvement in the severity of CD suggested an independent origin of motor disturbances [28]. Furthermore, in another study, depression severity does not correlate with the dystonia severity nor does depression improve when dystonia is treated [15]. Thus, depression appears to be a feature of the clinical spectrum of focal dystonia and not just a reaction to motor symptoms. The pathophysiology underlying both motor and non-motor symptoms, however, remains poorly understood [38].

In addition, Heiman et al. revealed that the risk for early-onset, before 30 years, recurrent major depression was increased in both manifesting and non-manifesting DYT 1 mutation carriers compared to that in non-carriers. The severity of dystonia in manifesting carriers was not associated with the likelihood of major depression, and mutation carriers did not have an increased risk for other affective disorders. This lead to the conclusion that early-onset recurrent major depression is a clinical expression of the DYT 1 gene mutation that is independent of the motor disturbance. DYT 1 gene is likely involved in dopamine release or turnover, thus suggesting a link between basal ganglia disease and depression [34]. Functional imaging confirmed that striatofrontal circuits playing a role in the mood and behavior regulation might be affected in dystonia patients. They have shown that these non-manifesting carriers have a decreased D2 receptor binding in the basal ganglia [39] and hypermetabolism in the putamen, anterior cingulate, and cerebellar hemispheres [40].

Deep-brain stimulation (DBS) of the internal globus pallidus deserves special attention for its effect on mood. While most studies suggest that DBS for dystonia results in mildly improved or unchanged measures of depression [41], worsened mood and suicide have also been reported [42, 43]. Most of the patients who committed suicide, however, had an excellent motoric response from stimulation, providing further evidence that the severity of dystonia may not correlate with symptoms of low mood [15].

2.1.2. Treatment options

For treating comorbid depression, tricyclic antidepressants (TCAs), monoamine oxidase inhibitor (MAOI), and selective serotonin reuptake inhibitor (SSRI) could be administered. However, an important factor is the association between these agents and reversible drug-induced dystonia which occurs more commonly with SSRIs [8]. If antidepressant therapy worsens dystonia, changing to a different class of drug, or adding in an anticholinergic may, minimize, or prevent exacerbation of dystonia [8]. Cognitive-behavioral therapy (CBT) might ameliorate depression in dystonia patients by altering maladaptive coping strategies that contribute to the mood disorder [35].

2.2. Anxiety disorders

2.2.1. Epidemiological and etiological basis

In contrast to some studies that did not show a difference in anxiety scores between patients with isolated focal dystonia and controls [12, 13, 20, 21, 44], an increased frequency of anxiety disorders especially obsessive–compulsive disorder (OCD), social phobia, and panic disorder in patients with isolated focal dystonia, and predominantly CD, has been highly reported, though studies have some limitations [10, 14, 16, 17, 30, 31, 36, 45–50]. A matter of interest is the study conducted by Lencer et al. who described the personality profiles of isolated focal dystonia patients, affected of psychopathology as well, using a 5-Factor Personality Inventory —NEO-FFI [10]. A high lifetime risk for psychiatric or personality disorder (70.9%) in CD and BS was observed. An increased lifetime risk for the development of social phobia (OR 21.6; 23.3%), agoraphobia (OR 16.7; 10.5%), and panic disorder (OR 11.5; −0.8%) was found, as well as an increased prevalence rate of 32.6% for anxious personality disorders comprising OCD (22.1%) and avoidant personality disorders—specific phobia (16.3%), alcohol abuse (15.1%), and drug dependence (2.3%) compared to general population [10]. Anxiety disorders (except for social phobia), manifested prior to the occurrence of dystonia symptoms [10], were broadly reported [10, 17, 47]. When investigating the personality traits, focal dystonia patients demonstrated pronounced agreeableness, conscientiousness, and reduced openness. For conscientiousness, increased scores were observed without gender difference, indicating obsessive orderliness and perfectionism [10]. Similar personality profile with increased perfectionism and obsessiveness was found in dystonia-affected musicians, compared with non-dystonic musicians [14]. Trait anxiety was also increased in patients with focal hand dystonia as compared to a healthy case–control group [51]. These findings lead to a discussion that dystonia patients might share similar personality traits, which is more likely to reflect a common neurophysiological pathway. Besides, these personality traits are seen as long-term predispositions and are therefore likely to be present prior to the onset of dystonia. The repeated [11] observation that anxiety disorders preceded the motor dysfunctions in a majority of cases gives another argument to the presumption that primary focal dystonia might be viewed as a neuropsychiatric disorder rather than a pure movement disorder [10, 11, 51]. Furthermore, the 1:1 ratio of men to women affected may indicate that psychopathology is likely related to the pathophysiology of isolated focal dystonia, as in the general population, women usually show twice the rate of anxiety and major depression disorder diagnoses when compared to men [10, 11]. It might be presumed that the typical for dystonia disturbance of neural activity in motor loops, linking the basal ganglia via the thalamus to the frontal cortex, may also have an influence on the limbic loops which mediate attentional, cognitive, and limbic functions resulting in both altered motor and affective processing [52]. The link between networks subserving mental and motor functions may be provided by a direct affective input to the caudate nucleus and the thalamus originating from the amygdale and the orbitofrontal cortex. Dysfunction of the basal ganglia-thalamo-cortical circuits has been assumed to underlie both motor and psychiatric symptoms [53]. Similar hypothesis was supported by a recent study, comparing the prevalence rate of psychiatric disorders among different movement disorders, namely isolated focal dystonia, monogenic, and idiopathic Parkinson's disease [23]. Each

movement disorder appeared to present with different psychiatric comorbidity profile, with isolated focal dystonia expressing the highest rates of anxiety disorders (OR = 3.3). These findings suggested that psychiatric disorders be a part of the phenotypic spectrum of movement disorders with each associated with specific psychiatric disorders indicating disturbances in a different neural circuitry for sensorimotor control [23]. Affective or stress-related factors might modulate cerebral sensorimotor representations through interactions between limbic and sensorimotor networks, which could explain the observation that dystonic symptoms can be triggered by emotional stress [23, 54]. These considerations suggest that anxiety disorders, OCD, and other stress-related disorders share common alterations in sensorimotor systems with isolated focal dystonia [23].

A recent study in the Chinese population reported a higher prevalence for anxiety in CD (28.3%) and in BS (20.0%) patients, with no differences in the anxiety scores between the two dystonia subtypes, and no significant correlations between motor symptoms and anxiety scores, thus pointing toward an independent course of both conditions [26]. By contrast, Berman et al. investigated 478 adult-onset focal dystonia, where anxiety and social anxiety severity vary by onset site of focal dystonia, with higher anxiety in cervical and laryngeal, lower anxiety in upper cranial, and higher social anxiety in laryngeal, suggesting distinct psychopathology depending on the initial body region affected by dystonia [38]. However, the commonly observed social anxiety (31.7–72.7%, depending on the site of dystonia onset) might be associated with altered body image and attitudes toward illness, but not dystonia severity [38]. Further, a rapidly increasing positive relationship between the severity of dystonia and social anxiety in the laryngeal onset group was found, suggesting that speech difficulties in particular may lead to secondary stigma and social anxiety [38]. Another factor for developing a secondary social anxiety (social phobia) may be the pronounced personality traits of patients with focal dystonia, facilitating difficulties in coping with dystonia symptoms and thus avoid social situations and being evaluated by others [10]. In a study of 116 CD patients, a 71% lifetime prevalence of social phobia was found and it correlated with body image, and a "maladaptive attitude" toward their illness, and not the objective severity of the dystonia [36]. Much like depression and other forms of anxiety, one can hypothesize that self-esteem and body concept play an important role in the development of social phobia [36]. On the other hand, several studies suggest that social phobia occurs at increased rates in primary focal dystonia [10, 16, 36], even more common than in other possibly stigmatizing disorders such as alopecia areata and thus is unlikely to be a mere consequence of disfigurement [36].

The reported increased chances for alcohol abuse and drug dependence in men may be a consequence of the fact that motor symptoms in dystonia may be relieved by alcohol, benzodiazepines, or anticholinergic drugs [36, 38]. Interestingly, results from genetic studies suggest that there may be an additional neurobiological factor predisposing to substance-related disorders in primary focal dystonia [55, 56]. Genetic factors may be another shared neurobiological basis. Although beyond the scope of isolated dystonia, an interesting example is the finding that patients with myoclonus dystonia suffered more frequently from OCD and alcohol abuse, which might be partly caused by the mutation of epsilon-sarcoglycan (*SGCE)* gene [55, 56]. A confounding factor, however, might be that myoclonus dystonia improves with

alcohol, and this could be the reason for the higher alcohol dependence [15]. By contrast, no evidence suggesting a higher risk of anxiety disorders in DYT1 carriers was found [57].

Particularly interesting is the connection between OCD and isolated focal dystonia. A large recent study revealed that clinically significant obsessive–compulsive symptoms are over-represented in isolated focal dystonia as compared with both HFS and healthy controls [50]. Besides, OCD caused great disability and significant impact on quality of life [50]. Another study also confirmed obsessive–compulsive symptom scores above cutoff for clinical significance in patients with primary focal dystonia (CD, BS, and writer's cramp) when compared to healthy and chronic illness controls, with predominantly developed hygiene-related symptoms [20]. It remains unclear why obsessive–compulsive symptoms are not universally present in primary focal dystonia, but reported results might suggest a common neurobiological basis related to cortical-basal dysfunction [46]. On the other hand, a study, although small-sampled, found OCD to be increased both in focal dystonia and in HFS, compared to healthy controls, but with significant between groups thematic content, and usually with mild severity [58]. No significant differences in obsessive–compulsive symptoms emerged in a study comparing DYT1 carriers to a control population [57].

In summary, depression appears to be more likely to represent a primary feature of isolated dystonia, whereas other psychiatric abnormalities have a less certain relationship and require additional evaluation [15].

2.2.2. Treatment options

There are no specific guidelines or published pharmacological treatment trials of psychiatric illness in the context of isolated dystonia, and treatment is based upon regimens used in non-dystonic patients [11]. However, when treating comorbid psychopathology, certain modifications to standard regimens must be made to take account of issues of treatment safety and efficacy in patients with dystonia [8]. The core treatment for social phobia and panic disorder may rely on CBT with or without an SSRI, bearing in mind the potential of SSRIs to exacerbate dystonia [8]. CBT has an uncertain effect for social phobia in dystonia patients as they may genuinely experience excessive scrutiny and criticism in social circumstances because of their appearance [59]. A case report describes the efficacy of CBT in alleviating symptoms of CD [60], and another recent study reported satisfactory results in treating non-motor symptoms in dystonia patients with combined CBT and mindfulness program. An interesting fact is that benzodiazepines, often used in treating the motor symptoms, because of their muscle relaxation properties, have not been described with their known anxiolytic effect in primary dystonia [11]. For the treatment of OCD in dystonia patients, Exposure and Response Prevention (ERP), a technique in which the patient is repeatedly exposed to situations that provoke the ritualistic behavior and instructed to resist performing them, may be tried. Although evidence is insufficient, a single case report showed ERP effective in treating OCD associated with dystonia secondary to basal ganglia infarction [61]. Minding the disabling nature of OCD and safety of ERP, this treatment should be trialed in the cases of comorbid OCD [8]. There is an emerging need to examine the effects of psychiatric treatment on both motor symptoms and mental and physical aspects of quality of life. Such multidimensional approaches are necessary to improve the objective and subjective well-being of patients with dystonia [11].

2.3. Other psychiatric disorders

Beyond the spectrum of mood and anxiety disorders, but in line with the hypothesis of shared neuroanatomical pathways, psychotic features, not related to therapy, in patients with idiopathic dystonia were observed [20, 24], suggesting a probable common dysfunction of the cortico-cerebello-thalamo-cortical projections [24], although other studies did not find psychotic symptoms in dystonic patients [23]. Patients with CD may have difficulty identifying angry faces when compared to age-matched controls [62] or to identify auditory expressions of disgust [63]. These separate lines of evidence suggest an interesting association between dystonia and longstanding emotional processing deficits; however, the exact interplay between these symptoms is not clear [11].

2.4. Psychiatric disorders and quality in life in dystonia patients

Emerging data highlight psychiatric comorbidity, namely depression and anxiety, as the most important predictor of poorer health-related quality of life (HRQoL) in patients with focal and especially cervical dystonia [9, 64–66]. A recent study revealed that the first eight domains of HRQoL were significantly lower in dystonia patients compared to that in controls, and this strongly related to the presence of depressive and anxiety symptoms, pain, and disability, while there was no significant correlation with the objective severity of motor symptoms. The degree of disability was only predicted by the degree of pain and depressive symptoms, and pain was mostly associated with disability and anxiety symptoms [9]. These findings suggested psychiatric comorbidity as the most important predictor of a decreased HRQoL and argues against a decreased HRQoL as a sole consequence of living with a chronic, visible, and disabling movement disorder [9]. Similar data were reported in a number of previous QoL-related surveys [64–66]. In another recent large study on QoL of 96 CD patients, five components (disability, psychiatric features, pain, physical function, and severity of dystonia) explained 74.4% of the variance in disability. Psychiatric features had the largest contribution to disability, followed by pain, physical functioning, and severity of dystonia which had no significant contribution [29].

All these findings lead to the need for a systematic screening for psychiatric disorders in dystonia patients, as well as novel treatment strategies to be implicated for copying psychiatric problems in dystonia patients in order to improve disability levels and health-related quality of life.

3. Cognition

Etiology and pathophysiology of isolated dystonia remain incompletely understood, yet dystonia is associated with basal ganglia dysfunction, and there is growing evidence that the basal ganglia plays a role in both cognitive and motor functions, supported by neuroimaging studies, revealing changes in non-motor areas and the cortico-striatal-thalamo-cortical circuits in dystonic patients [67]. However, evidence supporting cognitive impairment in primary dystonia is limited and contradictory [68].

Allam et al. assessed nine patients with primary cranial dystonia and found a sustained attention deficit in patients, compared with health-matched controls, despite well-preserved intellectual skills. BoNT treatment improved concentration endurance (sustained attention) to control values, suggesting that executive dysfunction in CD could be a secondary phenomenon, due to the disrupting effects of dystonia [69]. A constellation of attentional-executive cognitive deficits was confirmed by another study, assessing patients with young-onset generalized (both DYT 1 positive and negative) and adult-onset focal and segmental dystonia and healthy controls with the Cambridge Neuropsychological Test Automated Battery, although interpretations might by confound by the heterogeneity of the group and concomitant therapy with dopaminergic and anti-cholinergic medication [70]. The speed of information processing, language, spatial, memory, and general intellectual skills were well preserved [70]. Aleman et al. reported disturbed attention skills and a decreased capacity of performing complex motor tasks involving coordination of both hands in BS patients, compared to matched controls, revealing a cognitive impairment, independent from depression, anxiety, and premorbid intelligence. These findings were not dependent on symptom severity or disease duration, strongly suggestive of broad cortical involvement, including prefrontal and parieto-occipital dysfunction in focal dystonia [71]. In addition, the authors observed that BS patients made, although not statistically significant, more errors and more perseverative answers on The Wisconsin Card Sorting Test (WCST) than expected according to population means [71]. Several other studies support the evidence that when compared to healthy controls, patients with primary dystonia performed worse on the WCST [69, 72]. Assuming that the impairment of executive functions in dystonia patients might be partially due to some confounding factors such as depression or symptom-related distraction, Lange et al. compared the BS patients results achieved on the WCST, with the results of HFS patients. Furthermore, the authors compared global cognitive functioning, psychiatric symptoms, health status, and impulsiveness in both groups, thus trying to eliminate confounding factors. BS patients committed significantly more errors on the WCST, suggesting that cognitive inflexibility in idiopathic BS patients results from the specific pathophysiological processes underlying primary dystonia, which may arise from changes in cortico-basal ganglia circuits [73]. By contrast, when assessed with the Frontal Assessment Battery, executive function was not altered in BS compared with HFS [74]. Another study of 10 patients with primary dystonia, who differed in terms of body distribution, did not reveal any deficits in executive function or working memory either, but observed significantly lower word fluency than the healthy controls [75]. A set of neuropsychological tests was administered to non-depressed, non-demented patients with cranial-cervical dystonia and healthy control subjects. Patients with cranial-cervical dystonia showed deficit on working memory, processing speed, visual motor ability, and short-term memory, suggesting cortical and subcortical changes in the basal ganglia-thalamo-cortical circuits and their functional subdivisions of the oculomotor, prefrontal, and cingulated circuits that play an important role in executive functions, visual reproduction and visual–spatial coordination, working memory, attention, learning, and potentiating behavioral-guiding rules [76]. Such findings were confirmed in a recent large study of 68 primary BS patients and matched controls. The prevalence of cognitive deficits varied between 22.0% measured by the Mini-Mental State Examination (MMSE) and 32.3% measured by Addenbrooke's Cognitive Examination-Revised (ACE-R). The most frequently affected domains were visuospatial

function (30.9%) and language (30.9%), followed by memory (27.9%), orientation/attention (26.4%), and verbal fluency (22.0%). Patients with cognitive deficits showed lower QoL, especially in the subdomains of physical and social functioning, as the poor performance on the ACE-R was related to poorer QoL [68]. Another recent study investigating 60 CD patients, 60 BS patients, matched with 60 controls, found poor cognitive performance in 25% of CD and in 35% of BS patients assessed by ACE-R, with a lack of correlation between cognitive performance and severity of motor symptoms, suggesting that cognitive decline may be a clinical expression of dystonia [26]. By contrast, in non-DYT 1 primary generalized dystonia, no cognitive deficit compared with healthy controls has been detected in two studies [77, 78], and no cognitive abnormalities have been found in either manifesting or non-manifesting DYT 1 gene carriers [79].

In summary, the available data are contradictory ranging from subtle or no alteration of cognitive functions in primary dystonia [79], to cognitive impairment, influencing patients' QoL [68]. However, the most reported cognitive deficits are in the area of attention [68–71], executive functions [70, 76], word fluency [68, 73, 75], and visuospatial domains [68, 76]. The second contradictory is related to the etiology of the available cognitive impairments—whether they represent a part of the disease or a secondary alteration. Indeed, some may be related to the distracting effects of abnormal movements and pain, which may impair attentional processes, tending to improve with dystonia treatment [69]. Comorbid depression and anxiety (OCD), the use of some medications (e.g., anticholinergic) may also affect the cognition [80]. On the other hand, recent studies consider these factors and tried to avoid them in their study design and consecutive analyses [68, 71, 73, 76]. The limitation with most studies is the small sample size, and in some of them combining dystonia subtypes [69]. The different sensitivities of the neuropsychological batteries adopted in these studies with different research focuses and the use of different control groups may have also contributed to the inconsistent findings and hindered the cross-study comparisons [68].

4. Sleep disturbances

4.1. Impaired sleep quality (self-reported)

Most of the available studies reported an increased rate in impaired quality of sleep (QoS) in isolated/primary focal [26, 81–84], segmental, and generalized dystonia when compared to healthy controls [81]. The prevalence rate, dependent on the different studies for focal dystonia ranges, between 36 [26] and 45%, as most studies focused on CD and BS patients [82]. Although differences in QoS scores in CD patients might be partly confounded by depression, the differences QoS scores in BSP were not influenced by Beck Depression Inventory [83]. An impaired QoS was observed more frequently in CD compared with controls, even when controlling for the effects of depression, anxiety, and benzodiazepine use [84]. CD patients suffered worse QoS than BS patients, which might be partially due to pain, common in CD but absent in BS [26, 83]. The predictors for worsened QoS were mostly associated with depression (26%), restless legs syndrome (19%), and bruxism (in CD), but not severity of dystonic

symptoms [82]. Lack of correlation between QoS and severity of dystonia in both CD and BS patients suggested that insomnia might be a comorbidity disorder in patients with BS or CD [26, 83], pointing to an intrinsic mechanism of sleep disturbances rather than a direct effect of dystonic muscle activity [82]. Furthermore, QoS did not improve following BoNT treatment, despite a robust improvement in CD severity. This dichotomy suggests that sleep aberrations in CD require separate focus for effective treatment and cannot be viewed as secondary complications of the motor elements of this condition [84]. Although insomnia showed a tight connection with depression, the causal relationship between QoS and depression remains unknown. Overall, insomnia might be a feature of primary cranial and cervical dystonia [26, 83]. Nocturnal sleep disturbances correlated significantly with the HRQoL. They negatively impacted the QoL even when controlled for comorbid depression [81], suggesting that the assessment and treatment of insomnia-related complaints should be considered in global management plans of patients with dystonia [83].

4.2. Excessive daytime sleepiness

Excessive daytime sleepiness was not as common as QoS impairment, with a frequency varying from 6 [82] to 27% [81], depending on the study sample and design. Some studies failed to find a significant difference in daytime somnolence compared to the healthy population [82, 84], although a higher percentage of daytime sleepiness, measured by Epworth Sleepiness Scale (ESS), was found in CD patients, compared with both healthy controls and patients with other focal movement disorders [85]. A critical evaluation assesses the use of anticholinergic medications that may account for some but not all of this increase in sleepiness in the CD group. Disease severity and other common medication use (benzodiazepines, antidepressants) were not associated with increased ESS scores [85]. No improvement in daytime somnolence was observed with BoNT treatment, despite improvement in CD severity [84]. The excessive daytime somnolence correlated significantly with the HRQoL; however, these effects were not observed when controlled for depression [81]. These preliminary findings on daytime sleepiness suggested that further investigation into disordered sleep is warranted [85].

4.3. Polysomnography

In several studies of severely involved patients with dystonia musculorum deformans, the polysomnographic findings were characterized with increased latency to sleep, with a specific pattern of spindle activity, characterized by pronounced, high-amplitude spindles that were continuous for all stage 2 and portions of stage 3 sleep, and reduced sleep efficiency, suggesting a clinical significance [86, 87]. These findings, however, were not confirmed in further polysomnographic investigation [88]. Abnormal movements in patients with Meige's syndrome and BS appeared to be present during sleep but decreased in frequency and amplitude in all sleep stages. [89], whereas in CD patients, though sleep architecture was significantly affected (with a decreased sleep efficiency and an increased sleep latency), activity over cervical muscles disappeared during all the sleep stages, reaching significantly decreased values when compared to healthy controls. Thus, the reported poor QoS and impaired sleep architecture in CD cannot be related to the persistence of muscle activity over the cervical muscles [90]. These findings elicit

the need of further studies on sleep, including polysomnographic investigations in patients with different types of dystonia [91].

4.4. Fatigue

Besides sleep disorders, a large study on focal, segmental, and generalized dystonia observed moderate to severe fatigue in 43% that significantly correlated with HRQoL even when controlled for depression and sleep disturbances. The symptoms of fatigue persisted despite improvement of motor symptoms after BoNT treatment [81]. Subjective ratings of both energy and tiredness associated with HRQoL even when controlling for depression were reported in another study [92]. In dystonia, the frontal and subcortical circuits are known to be dysfunctional as seen in fatigue. Thus, a hypothesis of possible overlap in pathophysiology at a central level was proposed [81]. Notably, pain was correlated with fatigue but not sleep or sleepiness, supporting the dissociation of these constructs and suggesting a potential contributory role [81].

In summary, it seems that sleep impairment may be a feature of primary dystonia that is independent of the severity of the motor symptoms of the disorder. It is, however, correlated with depression, and therefore it is not clear at present if there is a primary sleep abnormality in dystonia [15]. Secondary effects of pain and medications also may play a role in the etiology of sleep disturbances [80]. Further studies on sleep including polysomnographic recordings are warranted to address this issue. And finally, sleep needs to be targeted in therapy. Preliminary evidence suggests that sleep is not sufficiently improved after BoNT treatment, thus QoS should be included as an outcome in treatment studies. If the finding that sleep is not improved after state-of-the-art treatment is replicated, standard sleep treatments such as CBT and the newer forms of behavioral therapy for insomnia need to be evaluated and, if necessary, adapted for patients with dystonia [91].

5. Sensory disturbances

One characteristic feature of idiopathic focal dystonia is the role of sensory feedback that manifests as the phenomenon of geste antagoniste or “sensory tricks,” which refers to various maneuvers used by patients with focal dystonia to temporarily relieve their dystonic spasms, offering a strong evidence that dystonia is also a sensory disorder [93]. On the other hand, sensory stimulation might trigger dystonia, for example, a loud noise producing spasmodic torticollis. Sensory symptoms may also precede the onset of dystonia or develop concomitantly [25, 93]. Abnormal sensory input might be as well a trigger for dystonia. Trauma to a body part is often a precedent to dystonia of that part, grittiness or dryness of the eyes is common in blepharospasm [25, 93].

Sensory function, particularly in the somatosensory domain, has been shown to be compromised in patients with primary dystonia, both in adult-onset focal forms and in genetically characterized DYT 1 dystonia [94, 95]. Studies have revealed evidence of abnormal somatosensory spatial and temporal discrimination, higher in dystonic patients than in healthy subjects [94–98].

Temporal discrimination is the shortest time interval for which two successive stimuli are perceived as separate. This is essential for somatosensory functions such as kinesthesia, graphesthesia, vibratory sense, and stereognosis [93]. Temporal discrimination is impaired in patients with dystonia, and the deficit is more pronounced in focal dystonia compared with the generalized form [93]. Bradley et al. found abnormal temporal discrimination threshold (visual, tactile, and mixed) in 97.3% of CD, 85.7% of writer's cramp, 88.8% of BS, 90.1% of spasmodic dysphonia patients, and in 62.5% of musician's patients. The sensory abnormalities were also present in unaffected relatives, possibly indicating a non-manifesting gene carriage [96, 97]. Given that nonaffected DYT 1 gene carriers may show similar abnormalities to clinically affected individuals, sensory deficits could constitute a subclinical endophenotypic trait of disease that precedes overt clinical manifestations [95]. Proprioceptive afferent-related functions, and particularly kinesthesia and vibration-induced illusion of movement, are abnormal in patients with focal dystonia. This abnormality occurs in both affected and unaffected body regions with similar results being reported in asymptomatic first-degree relatives [25]. The degree of temporal discrimination impairment is positively correlated with the degree of severity of dystonia. This discrimination deficit was identified in both the affected and unaffected hand, implying that the deficit is a result of a central process of dystonia itself, rather than a byproduct of the abnormal muscle contractions [99, 100].

Spatial discrimination differentiates two spatially separated stimuli and is measured as the shortest distance between the stimuli that are perceived as separate [93]. Altered spatial discrimination thresholds are found in familial and sporadic adult-onset focal dystonia patients and in some unaffected relatives who may be non-manifesting gene carriers [101]. Molloy et al. also find spatial discrimination to be impaired in affected, as well as in clinically normal body regions for a wide range of focal dystonia, but not affected in generalized dystonia, suggesting either partially separate pathophysiologic processes in both subtypes of dystonia, or early adaptive changes or compensatory mechanisms in generalized dystonia [94].

Further evidence of the involvement of the sensory system in dystonia comes from a number of studies that have investigated mechanisms of synaptic plasticity in cortical sensorimotor areas by means of transcranial magnetic stimulation. These neurophysiological studies have revealed impaired cortical somatosensory processing, which may be due to an abnormal inhibitory interneuron activity and abnormal sensory motor integration in patients with dystonia [25].

In summary, sensory symptoms and sensory system abnormalities are present in dystonia patients. Sensory symptoms may also precede the onset of dystonia [25]. Neurophysiological studies revealed defects of temporal and spatial discrimination, of integration of sensory stimuli, and of proprioceptive afferent processing as well as movement representation which have been observed not only in affected body parts but also in those remote from dystonic symptoms. This finding reflects diffuse neurophysiological and neuroimaging sensorimotor abnormalities reported in dystonia regardless of the clinically affected body part [25, 95].

On the basis that there may be abnormalities in processing somatosensory inputs, several neurorehabilitative approaches have been developed including upper limb or finger immobilization, sensorimotor training, and transcutaneous electrical nerve stimulation. Although the

real efficacy of these treatments has yet to be confirmed in randomized, blinded, and controlled studies, it may be that rehabilitation of the somatosensory processing improves motor symptoms. This could provide efficient strategies to aid functional recovery, mainly in focal hand dystonia, in which the available medical treatments offer little benefit [95].

6. Pain

Pain is one of the most common complains in dystonic patients, reaching approximately 84% of CD patients and a major source of disability [102]. Although commonly associated with CD, significant pain may be reported by patients with BS, masticatory dystonia, and limb dystonia. In some patients with cervical dystonia, pain is much more debilitating than abnormal head postures [103].

One potential reason for pain to be so prevalent in dystonia may be a reduced stimuli threshold [104]. Patients with dystonia may also have alterations in pain processing even in body parts without dystonic involvement [104]. Another potential mechanism for excessive pain includes alterations in the somatosensory system. Ongoing depression, common in this population, correlates with symptoms of pain [80], but pain intensity often correlates poorly with the severity of dystonic contractions or amplitude of involuntary movements [6]. Lastly, sleep itself may mitigate against pain [80].

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 BoNT [80].

7. Autonomic dysfunction

In dystonia patients, most of the autonomic dysfunction is related mainly to treatment with anticholinergic medications or BoNT, and especially with BoNT B, although Tiple et al. found that CD patients have mild, subclinical abnormalities in autonomic cardiovascular regulation, heart rate and systolic blood pressure variability, and cardiopulmonary baroreflex sensitivity prior to therapy, which do not worsen after BoNT-A injection [105]. Tinter et al. reported patients treated with BoNT-B to have less saliva production and greater severity of constipation, than those treated with BoNT-A [106]. Another study of CD patients reported that BoNT side effects consisted of dryness of mouth, accommodation difficulties, conjunctival irritation, reduced sweating, swallowing difficulties, heartburn, constipation, bladder voiding difficulties, head instability, dryness of nasal mucosa, and thrush, again, occurring far more often after BoNT-B than after BoNT-A, suggesting a systemic spread of BoNT-B [107].

A special interest is that reported by Hentschel et al. where cardiovascular autonomic imbalance with sympathetic predominance occurs as a non-motor manifestation of CD, associated

to comorbid depression. A decreased heart rate variability and orthostatic hypotension were observed at a significantly higher rate when CD was combined with a mood disturbance, without other significant differences in autonomic function [108]. These results draw attention to the need to identify and treat depression in dystonia.

8. Conclusion

Isolated, previously defined as primary dystonia, appeared to be no longer accepted as a solely motor manifestation, but a number of evidences pointing toward a disturbance in many non-motor domains emerged through decades. Most of the studies available focused on the examination of the coexisting mood and anxiety spectrum disorders and disturbance in the sensory system, but sleep and cognition disruptions have also been reported at a higher rate. There are still controversies as to whether non-motor symptoms reflect a secondary dysfunction to the motor impairment or share common etiological and pathogenetical mechanisms with the dystonic disorder. The exploration of future therapeutic approaches should be focused not only on treating the movement symptoms but non-motor presentations as well. Future investigations in the field of epidemiology, etiology, and treatment of non-motor symptoms in isolated dystonia are warranted in order to enlighten the bizarre nature of this movement disorder.

Author details

Nikolina I. Semerdjieva* and Ivan G. Milanov

*Address all correspondence to: nikolina.semerdjieva@gmail.com

University Hospital “St. Naum”, Sofia, Bulgaria

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