

# Cervical Dystonia and Depression: Which Comes First?

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## Introduction

Dystonia is characterized by sustained or intermittent muscle contractions that cause abnormal movements and postures. According to a recent consensus paper of the Movement Disorders Society, the clinical classification of dystonia is based on two axes [1]: Axis I describes the clinical characteristics and phenomenology of various dystonias, while Axis II takes into account the aetiology. Cervical Dystonia (CD) is one of the most common forms of adult onset dystonias [2] and is characterized by an excessive activity of neck muscles leading to abnormal head movements and postures. Disability in CD arises mainly as a consequence of motor disturbances. Recent evidence, however, shows that in addition to motor abnormalities, patients with CD also have several Non-Motor Symptoms (NMS) including pain, sensory abnormalities and psychiatric disturbances [3-5]. Several studies have consistently reported that CD patients have a high frequency of depressive and anxiety disorders [3,4,6] and these disorders have a profound impact on the quality of life [7,8]. It is however still unclear whether depression emerges in CD patients as a consequence of the burden of motor disturbances, or whether it should be considered part of the spectrum of this disorder. The aim of this paper is to review studies investigating psychiatric disorders (with emphasis on depressive disorders) in patients affected by CD, and to see whether depression should be considered an intrinsic symptom of the neurological disease.

## Psychiatric Disorders in CD

The frequency and type of psychiatric disorders in CD has been addressed in several studies [6,9]. Comparison between studies may however be difficult because researchers have used different methods to diagnose the various psychiatric disturbances (i.e., Formal Interview vs Self-Rating Scales), or because not all studies compared the results with those obtained in healthy control

subjects. Notwithstanding these limitations the results of the majority of studies confirm that psychiatric disorders are frequent in CD. For example, diagnosis of current or lifetime psychiatric disorders was found in up to 91.4% of patients with CD, as compared to 35% in the general population [10]. Specifically, CD patients have an increased lifetime risk of developing depression (ranging from 15% to 53.4%) and anxiety disorders (ranging from 26.4% to 83.3%) [10]. Lencer et al., in a comparison of the prevalence rates of psychiatric diagnoses in 86 patients with focal dystonia (70 with CD) with a reference population based sample (n = 3943), found a significant increase in lifetime prevalence for any psychiatric or personality disorder (70.9 %) in dystonia patients [9]. In a case-control study that used the Standardized Clinical Interview for psychiatric Disorders (SCID-I), Fabbrini et al., [6] found that depressive disorders were significantly more frequent in CD patients than in age and sex-matched healthy controls (26.9% vs 6%,  $p < 0.01$ ); the Beck Depression Inventory (BDI) scores were also higher in CD patients than in controls ( $5.6 \pm 4.7$  vs  $2.8 \pm 2.2$ ,  $p < 0.01$ ). More recently, Lehn et al., confirmed that patients with focal dystonia (including CD) had more depressive, obsessive compulsive, and anxiety symptoms than either healthy subjects or patients with hemifacial spasm [11].

Further support for the high prevalence of psychiatric symptoms in CD comes from two recent studies. Comparing the prevalence rates of specific psychiatric disorders between different types of movement disorders, patients with focal dystonia (including those with CD) showed the highest rates of anxiety disorders [12]. Finally, Berman et al., [13], in a large (478 patients) international, multicentre cohort of recently diagnosed patients with adult-onset focal dystonia (including CD) determined whether the severity of psychiatric symptoms differs according to the initial site of onset. The results demonstrated that depression and anxiety (measured through BDI, HADS-D and HADS-A) coexisted in about one third of patients of isolated, idiopathic dystonia patients. The proportion

of patients with depression did not significantly differ across the different dystonia groups.

## CD and Depression: How are They Related?

Some studies have addressed the issue whether psychiatric disorders in CD patients are secondary to motor disturbances or whether they are part of the spectrum of this disorder. In 1998, Wenzel et al., [14] first showed that mood disorders preceded the onset of CD in 53% of patients, and that anxiety disorders preceded the onset of CD in 68% of patients [14]. Similar results were obtained a decade later by Moraru et al., [15], who found that 42.5% of their 40 CD patients met the criteria for at least one lifetime diagnosis of psychiatric disturbances prior to the onset of CD. In another study, a high prevalence of social phobia and depressive coping behavior was found to be the main predictor of psychiatric comorbidity in 116 CD patients [10]. In these patients, the mean age of onset was  $24.3 \pm 11.4$  years for psychiatric illness and  $42.5 \pm 14.4$  years for the onset of motor symptoms. The severity of depression in patients with dystonia, with the exception of one study [16], did not correlate with the severity of dystonia, suggesting that depression is a primary abnormality [4,17]. Fabbrini et al., [6] also confirmed that psychiatric disorders started on average  $18.4 \pm 13.9$  years before the onset of dystonia and that there were no clinic-demographic differences between CD patients with or without psychiatric disturbances. Following these observations, a recent five year long follow-up study of the psychiatric disorders in a cohort of CD patients, showed that depressive disorders are relatively stable during the course of the disease, in spite of an improvement in the severity of dystonia [18]. Finally, Muller et al., found that the treatment with botulinum toxin offers significant improvement in motor symptoms and pain relief in CD patients, but this improvement is not followed by an improvement in depression [19].

## Discussion

Most of the studies reviewed in this paper suggest that depression in CD is part of the clinical spectrum of the disorder. Supporting this hypothesis, we observed the following: 1) depression in many patients precedes the onset of CD; 2) the severity of depression does not correlate with the severity of dystonia; 3) there are no clinical-demographic differences between CD patients with or without depression; 4) psychiatric symptoms seem to be quite stable over the course of the disease in spite of an improvement in the severity of CD.

Pathophysiology of dystonia as studied by neurophysiological methods encompasses three main mechanisms: 1) lack of inhibition at spinal, brainstem and cortical level; 2) impairment of somatosensory processing and sensorimotor integration and 3) abnormal plasticity of sensorimotor cortex. Imaging studies also show changes in the basal ganglia-sensorimotor cortex network and in the cerebello-thalamo-cortical pathway. The pathogenesis

of depression in CD is still matter of discussion. Structural abnormalities in brain regions involved in emotion regulation have been reported in dystonia [20,21]. Adverse life events, dysregulation of monoamine neurotransmitter metabolism, genetic factors and activation of inflammatory pathways, including inflammatory cytokines are the main factors implicated in the aetiology of depression [22,23]. Cognitive and neurochemical abnormalities that are part of the complex domain of depression may trigger aberrant activity within the basal ganglia [24]. These mechanisms may have a role in the genesis of mood disorders in dystonia patients [25]. In addition, individuals with damage of basal ganglia often show changes in a variety of behavioral and psychological domains [26] including both emotion processing (e.g., perception and experience) [27] and increased risk for depression [28]. It is therefore possible that changes in the activity of cortico-striatal-thalamo-cortical circuits contributes not only to motor symptoms, but also to psychiatric symptoms in CD. A recent finding indicates that Striatal DAT BPND were significantly lower in depressed versus non-depressed CD patients, also suggesting a role for dopamine in the aetiology of depression in CD [29]. Clinical observation of the frequent co-existence of depression and anxiety in patients with CD, as well as the observation that cortical-limbic-striatal dysfunction is involved in depression and other neuropsychiatric disorders therefore suggests the direction of future research aimed at better characterizing relationship between CD and depression.

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