Aetiology of Co-morbid Psychiatric Disorders In Dystonia: A Biopsychosocial Hypothesis
A McNeill

Abstract
Dystonias are a heterogeneous group of movement disorders characterised by involuntary, sustained contraction of antagonist muscles that causes repetitive movements or abnormal postures. Dystonia is a rare condition. Nonetheless, it is important due to the high morbidity patient's experience. Much of this morbidity results from disability associated with dystonic movement. However, it is less recognised that the frequent occurrence of co-morbid psychiatric conditions (40 - 75% of patients) in dystonia contributes to the morbidity of dystonia. While the pathophysiological basis of dystonic movement has been extensively investigated, little research into the aetiology of co-morbid psychiatric disorders has been performed. Here, a literature review was undertaken to define what psychiatric disorders occur in dystonia and to find studies that could be synthesised into a Bio-Psycho-Social model of the aetiology of psychiatric disorders in dystonia. Current research supports the hypothesis that psychiatric disorders in dystonia result from both the underlying neurobiological abnormality and psychosocial factors associated with disability and disfigurement.

INTRODUCTION
The dystonias are a heterogeneous group of movement disorders, characterised by involuntary, sustained contraction of antagonist muscles, which results in twisting and repetitive movements or abnormal postures. Dystonias are classified on the basis of the muscle groups affected, or by aetiology, as outlined in table 1. Age at onset can also be used to categorise patients, since it provides prognostic information, with early onset (under 26 years old) cases often becoming generalised while late onset (over 26 years old) dystonia remains focal.

Epidemiological studies have demonstrated that the national prevalence of dystonia ranges from 127 to 329 per million globally, with an estimated 40,000 cases in the United Kingdom (U.K). Detailed epidemiological data for the U.K comes from the study by Duffey et al, which found a point prevalence of 14.28 per 100 000 for primary torsion dystonia, with a prevalence of 1.42 per 100 000 for primary generalised dystonias and 12.86 per 100 000 for primary focal dystonias. The most commonly encountered focal dystonias were Cervical Dystonia (CD) and Blepharospasm. U.K prevalence of secondary dystonia is unknown.
Thus, dystonia is a relatively rare condition, though of importance due to the severe morbidity that many patients experience, and the associated health care costs. Much of this morbidity clearly results from disability associated with dystonic movement. However, it is less appreciated that co-morbid psychiatric conditions occur frequently (3 – 6 times the level in the general population) amongst dystonia patients, and contribute significantly to their reduced quality of life. Co-morbid psychiatric disorders are defined as those that arise due to the effects of the movement disorder, and which are not merely present by coincidence.

The purpose of this paper is to review the dystonia literature in order to: 1. Define which psychiatric disorders occur in dystonia, 2. Evaluate the hypothesis that co-morbid psychiatric disorders are caused by both neurobiological abnormalities underlying dystonic movement and the psychosocial consequences of dystonia, 3. Identify issues of drug safety and efficacy that must be considered when treating co-morbid psychiatric disorders in dystonia.

**EPIDEMIOLOGY OF CO-MORBID PSYCHIATRIC DISORDERS IN DYSTONIA**

The Epidemiology of co-morbid psychiatric disorders is currently incompletely defined, as only small studies with highly selected patient groups have been performed. Nevertheless, the existing epidemiological data does provide an overview of the types of psychiatric conditions occurring in dystonia, and demonstrates a 3 – 6 fold increased prevalence of psychopathology compared with the general population.7

In CD 65 – 75 % of patients manifest at least one psychiatric disorder, with Unipolar Depression (47 %) being the most common diagnosis.7 A smaller proportion of CD patients have anxiety disorders (Panic Disorder 29.5 %; Social Phobia 41.3 %) or Obsessive Compulsive Disorder (OCD; 6.8 – 19.7 %).7 A high prevalence of depression has also been observed in blepharospasm (37 %) and axial dystonia (33 %), and in cervical dystonia secondary to stroke (20 %).9 Dystonia has also been associated with substance misuse (13 % of patients), especially in alcohol responsive myoclonic-dystonia.7 No studies have examined psychiatric morbidity in primary generalised or hemi-dystonia, or non-vascular secondary dystonias, but it seems likely these severe forms of the condition will have significant psychiatric co-morbidity.

It is noteworthy that the psychiatric disorder precedes dystonia onset in up to 40 % of cases,7 since this suggests the above studies may classify cases of psychogenic dystonia and coincidental psychiatric conditions as “co-morbid”, overestimating the prevalence of co-morbid psychopathology in dystonic patients. Nevertheless, given that psychogenic dystonia is rare and that the prevalence of psychopathology in dystonia greatly exceeds that in the general population, a significant proportion of psychiatric disorders in dystonia must be co-morbid (i.e. a consequence of the movement disorder). Treatment of psychotic disorders with drugs which act via dopamine antagonism causes Tardive dystonia in 5 % of patients, however, the studies cited in this paper excluded subjects treated with dopamine antagonists, and this form of co-morbidity is not discussed further here.

**EVIDENCE OF A ROLE FOR NEUROBIOLOGICAL FACTORS IN THE AETIOLOGY OF CO-MORBID OBSESSIVE COMPULSIVE DISORDER IN DYSTONIA**

Abnormalities of both cortical and basal ganglia function have been observed in patients with dystonia. It is currently proposed that abnormalities of cortical physiology in dystonia are secondary to a functional abnormality of the basal ganglia, since dystonic patients do not manifest signs of a pyramidal tract syndrome, and dystonic movements occur in disorders of the basal ganglia (e.g. Wilson's disease).10 Research demonstrating that certain primary psychiatric disorders are associated with physiological abnormalities of the basal ganglia lead to the hypothesis that a common neurobiological abnormality might cause both dystonia and co-morbid psychopathology.

The basal ganglia are composed of four nuclei lying deep to the cerebral cortex in each hemisphere that play a crucial role in the regulation of both voluntary movement and non-motor behaviour.12 The basal ganglia function by linking the frontal cortex and thalamus to form a group of five segregated parallel subcortical circuits. Emotional and executive aspects of behaviour are subserved by the three non-motor circuits outlined in Table 2, while the Skeletomotor circuit and Oculomotor circuit (which is not discussed here) regulate movement.12 Of the basal ganglia–thalamocortical circuits, it is dysfunction of the skeletomotor circuit that underlies dystonic movements13. Thus, before discussing the pathophysiology of dystonia it is important to detail the organisation and function of the skeletomotor circuit (Figure 1).
A variety of studies have demonstrated physiological abnormalities of the basal ganglia circuits in the absence of structural pathology in primary dystonia. For example, intraoperative recording of neuronal activity within the GPi in patients with primary dystonia undergoing pallidotomy revealed that mean discharge rates were significantly lower than normal, and that neuronal activity in the GPi was irregular – discharges occurring in sporadic bursts as opposed to normal tonic activity.\(^{15}\) It is hypothesised that a disruption of the balance of activity in the indirect and direct pathways linking striatum and pallidum underlies abnormal activity in the GPi.\(^{13}\) Indeed, recent positron emission tomography (PET) studies have provided evidence of increased activity in the direct striatopallidal pathway, while imaging studies showing reduction of D2 receptors in the putamen suggest reduced activity of the indirect pathway.\(^{13}\) Thus, there is clear evidence of dysregulation of GPi output in primary dystonia. However, explaining how this results in dystonic movements requires consideration of how disrupted GPi function might alter activity within motor cortical areas.

Functional imaging studies have generated a reasonably consistent picture of the motor cortical abnormalities that occur in dystonia. For example, in patients with generalised or focal arm dystonia, the medial and prefrontal cortical motor areas are overactive (increased regional cerebral blood flow [rCBF]) while the cingulate gyrus, caudal supplementary motor area, sensorimotor cortex and contralateral primary motor cortex are underactive (reduced rCBF) during voluntary arm movements.\(^{13}\) It is proposed that dysregulated activity of intra-cortical inhibitory interneurons, resulting from aberrant GPi function, is the basis of these changes in cortical activation levels.\(^{16}\) Thus, the decreased metabolic activity of inhibitory interneurons would cause reduced rCBF, and apparent underactivity, in certain cortical regions while resulting in increased activity of excitatory neurons and overactivity in other cortical areas.\(^{16}\)

The abnormal movements in dystonia are characterised by co-contraction of antagonist muscles and “overflow” of EMG activity into muscles that should not be activated during the movement.\(^{13}\) The altered activation pattern of the motor cortex could contribute to this, since abnormal motor planning, and impaired inhibition within the primary motor cortex, could result in inappropriate muscle activation during voluntary movement and involuntary posturing. The abnormalities of sensory feedback and spinal cord reflexes observed in dystonia also have a role in generating abnormal movements.\(^{14}\) However, as they are not relevant to the aetiology of co-morbid psychopathology they are not discussed here.

**THE ABNORMALITIES OF BASAL GANGLIA PHYSIOLOGY SEEN IN OCD & DYSTONIA ARE SIMILAR**

If the epidemiological association between dystonia and psychopathology were explained by both being induced by...
basal ganglia dysfunction then one would expect basal ganglia lesions to be capable of causing psychiatric disorders. Indeed, clinical reports indicate focal basal ganglia infarction can cause dystonia associated with new onset OCD or depression.\textsuperscript{1,7} However, as depression can occur after any stroke, it is probable co-morbid OCD, but not depression, results from a primary abnormality of the basal ganglia.\textsuperscript{17} Additional evidence that OCD and dystonia are aetiologically linked through dysfunction of the basal ganglia is provided by studies demonstrating a shared genetic predisposition to both OCD and primary focal dystonia,\textsuperscript{18} as well as by evidence that mutation of the DYT11 M-D gene causes the phenotype of dystonia and myoclonus combined with OCD.\textsuperscript{5}

Studies demonstrating that the abnormalities of basal ganglia physiology seen in primary OCD and dystonia resemble one another further support the contention that co-morbid OCD is induced by basal ganglia dysfunction. For example, PET studies of primary OCD have demonstrated hypermetabolism of the lateral orbitofrontal circuit of the basal ganglia,\textsuperscript{19} and transcranial magnetic stimulation (TMS) investigations have revealed a reduction in intra-cortical inhibition similar to that seen in dystonia.\textsuperscript{20} Furthermore, MRI evidence of neuronal loss in the striatum suggests that, as in dystonia, abnormalities of cortical physiology in primary OCD may be due to dysfunction of the direct/indirect Striatopallidal pathways resulting in aberrant activity of the Gpi.\textsuperscript{21}

Thus, it seems reasonable to suggest that dystonia with co-morbid OCD might result from a single pathological process that disrupts both the skeleton-motor and lateral orbitofrontal circuits of the basal ganglia to cause dystonia and OCD concomitantly. Why patients with OCD do not have an increased risk of developing dystonia is unclear. However, it might be explained by the hypothesis that in dystonia the genetic and acquired abnormalities can derange both skeleton-motor and lateral orbitofrontal circuits, while the genetic and environmental factors that cause OCD act at a point in the basal ganglia that can only disrupt the lateral orbitofrontal circuit.

EVIDENCE OF A ROLE FOR PSYCHOSOCIAL FACTORS IN THE AETIOLOGY OF CO-MORBID DEPRESSION & ANXIETY DISORDERS IN DYSTONIA

The major factors in the aetiology of depression are currently believed to be adverse life events and dysregulation of monoamine and dopaminergic neurotransmitter metabolism.\textsuperscript{23} Genetic factors also play an important role. It is proposed that cognitive and neurochemical abnormalities trigger aberrant activity within the basal ganglia,\textsuperscript{22} which contributes to the clinical features of depression.\textsuperscript{14} Research has shown that these mechanisms have a role in mood disorders in dystonia patients.

In depressed dystonia sufferers’ adverse life events involving loss, identified by Brown et al as specific precipitants of depression, are especially prominent. For example, 48% of patients leave paid employment as a result of their dystonia, 62% experience financial hardship and 29% report sexual problems.\textsuperscript{24} The disability caused by dystonia is also associated with psychosocial factors predisposing individuals to depression by reducing their ability to cope with “loss events”.\textsuperscript{23} Specifically, dystonia patients may become socially isolated and lack confidants – important “vulnerability factors” for development of depression.\textsuperscript{23} Moreover, the pain and disability of dystonia may act as a non-specific stressor and combine with other factors to induce depression.\textsuperscript{23} The aforementioned data come from large questionnaire surveys of dystonia patients in the U.K, and these figures are probably representative of the adverse effects of dystonia experienced by patients in Westernised societies.

There is also evidence that the neurobiological mechanisms underlying dystonia could induce depression by deranging monoamine metabolism. For example, decreased synthesis of monoamine neurotransmitters is thought to cause the rare disorder Dopamine-Responsive Dystonia (DRD), a syndrome of dystonia and psychiatric features such as depression that responds to L-DOPA treatment.\textsuperscript{25} The pathophysiological basis of DRD is known to be mutation of the Guanosine Triphosphate-Cyclohydrolase gene, which produces tetrahydrobiopterin (BH4), the cofactor required for the aromatic amino acid monoxygenases that synthesize monoamine neurotransmitters.\textsuperscript{26} The significance of reduced BH4 and monoamine synthesis in the genesis of neurological and psychiatric symptoms is emphasised by the observation that the severity of symptoms correlates with the degree of reduction of BH4 and monoamine metabolites in the cerebrospinal fluid of DRD patients.\textsuperscript{26}

There is no evidence from human studies that monoamine metabolism is deranged by the neurobiological abnormalities in primary dystonia. However, studies of a hamster model of primary dystonia have demonstrated altered levels of 5-
hydroxytryptamine and noradrenaline in the basal ganglia. This is significant as it suggests that monoamine metabolism may be abnormal in human primary dystonias, potentially predisposing to depression.

**ABNORMALITIES OF SELF-IMAGE & MONOAMINE METABOLISM UNDERLIE ANXIETY DISORDERS**

There is little direct evidence relating to why patients with dystonia should develop Social Phobia or Panic Disorder. Though it has been suggested that psychosocial factors and abnormalities of monoamine neurotransmitters are important. For example, the key causal factor in Social Phobia, a disorder in which the sufferer experiences inappropriate anxiety in social situations, is a cognitive distortion known as fear of negative evaluation, whereby the patient worries excessively that people will observe and criticise him. Thus, as many patients with Cervical Dystonia report feelings of embarrassment related to their appearance, an obvious consequence of dystonia is development of fear of negative evaluation and Social Phobia. However, why Panic Disorder should be so prevalent amongst individuals with dystonia is less apparent, though evidence suggesting abnormalities in 5-hydroxytryptamine and noradrenaline neurotransmission in both disorders implies a common underlying biochemical abnormality. It is important to note that in patients with Panic disorder or Social Phobia there is no increased risk of dystonia, this may be explained by the fact that the neurobiological processes underlying these conditions do not derange the function of the skeleto-motor circuit of the basal ganglia.

Thus, the occurrence of co-morbid anxiety and depressive disorders in dystonia may be accounted for by mechanisms similar to those that underlie these conditions when they occur as primary psychiatric disorders. Next, the severe impact that these co-morbid disorders can have upon dystonia patient's quality of life will be discussed.

**PSYCHIATRIC DISORDERS IN DYSTONIA: CLINICAL IMPORTANCE & TREATMENT OPTIONS**

Evidence for the clinical importance of co-morbid psychopathology in dystonia is provided by the social-epidemiological studies of Butler et al, which demonstrated that co-morbid psychiatric disorders can both directly and indirectly exacerbate the handicap experienced by dystonia sufferers. For example, many patients experience a “vicious circle syndrome”, where the onset of dystonia causes the development of anxiety and depressive disorders that can intensify the muscle spasm and so directly increase functional impairment. Even if anxiety, OCD and depression do not directly exacerbate dystonia they can cause additional disability by and of themselves that may critically impair the patient's already reduced ability to cope with day-to-day life. Furthermore, there is evidence that it is the presence of co-morbid psychiatric disorders, and not the severity of the movement disorder, which determines overall morbidity in dystonia. For example, studies utilising standardised questionnaires have shown that the presence of anxiety or depression is a stronger predictor of reduced quality of life scores than the severity of dystonia, while research in depressed dystonia patients treated with BOTOX has demonstrated that relief of the dystonia does not consistently increase quality of life. This evidence, combined with the fact that sustained relief of muscle spasm in dystonia is often impossible, lends support to the contention that attempts to improve the care of dystonia patients might profitably focus on treatments for co-morbid psychopathology.

Despite the clinical importance of co-morbid psychopathology, there are no specific guidelines for managing psychiatric disorders in dystonia, and treatment is based upon regimens used in non-dystonic patients. However, when treating co-morbid psychopathology certain modifications to standard regimens must be made to take account of issues of treatment safety and efficacy in patients with dystonia.

Successful treatment of co-morbid depression with a Selective Serotonin Reuptake Inhibitor (SSRI; Fluoxetine 20 mg O.D.) has been reported, though in theory other antidepressants of the Tri-cyclic (TCA) or Monoamine oxidase inhibitor (MAOI) classes could be utilised. However, an important factor, which is rarely mentioned in the literature, is the association between these agents and reversible drug-induced dystonia. This adverse effect occurs more commonly with SSRIs than TCA or MAOI anti-depressants, and patients with pre-existing movement disorders are especially vulnerable. Thus, when treating co-morbid depression use of an agent less liable to exacerbate dystonia, such as a TCA, should be considered, and careful monitoring of the patient for worsening dystonia instigated. Should antidepressant therapy worsen dystonia, changing to a different class of drug, or adding in an anticholinergic may, minimise/prevent exacerbation of dystonia. Though there is
no evidence to support its use, it has been suggested cognitive-behavioural therapy (CBT) might ameliorate depression in dystonia patients by altering maladaptive coping strategies that contribute to the mood disorder.\textsuperscript{38}

The core treatment for social phobia and panic disorder consists of CBT with or without an SSRI.\textsuperscript{19} However, it is unclear if CBT will be effective for social phobia in dystonia patients as they may genuinely experience excessive scrutiny and criticism in social circumstances because of their appearance.\textsuperscript{39} The potential of SSRI’s to exacerbate dystonia are a further problem.

Treatment for OCD is by a method known as Exposure and Response Prevention (ERP).\textsuperscript{19} In this technique the patient is exposed to situations that provoke the ritualistic behaviour and instructed to resist performing them, with repeated exposure and resistance the urge to perform the rituals will decrease and behaviour will normalise. There is little evidence to support the use of ERP in co-morbid OCD, though in a single case report ERP proved effective in treating OCD associated with dystonia secondary to basal ganglia infarction.\textsuperscript{40} Thus, given the disabling nature of OCD, and safety of ERP, this treatment should be trialled in all cases of co-morbid OCD.

CONCLUSIONS: AN ARBITRARY DIVIDE BETWEEN NEUROLOGY & PSYCHIATRY

Contemporary medicine cares for individuals with brain disease under two different disciplines.\textsuperscript{41} Patients who suffer organic nervous system disorders are managed by Neurologists, while those with psychological disorders unrelated to obvious organic pathology fall under the auspices of Psychiatry. However, advances in neuroscience research demonstrating abnormalities of brain structure and function in Psychiatric disorders have lead to calls for a unification of Neurology and Psychiatry, with a return to the traditional discipline of Neuropsychiatry.\textsuperscript{41}

Much work has been done in conditions such as Parkinson's disease and Multiple Sclerosis showing that organic brain disease can cause both “Neurological” and “Psychiatric” symptoms in the same individual. In this paper I have performed a literature review to define possible aetiological factors causing co-morbid psychiatric conditions in dystonia patients. The diversity of possible causal factors cited in current research necessitates the use of a bio-psycho-social model to understand how a common neurobiological abnormality can cause dystonia and a range of co-morbid psychiatric conditions. Thus, the study of co-morbid psychiatric conditions in dystonia emphasises the need for multidisciplinary research in Neurology.

The results of this review also have implications for clinical neurology, since, because of the morbidity associated with co-morbid psychopathology, and the failure of treatments aimed at relieving muscle spasm, psychiatric interventions offer a promising therapeutic strategy for dystonia. This review has also highlighted gaps in our knowledge of psychiatric co-morbidity, and, because of potential clinical benefits, it is clear that studies of the safety and efficacy of pharmacological interventions for psychopathology should be a high priority in future dystonia research.

SEARCH STRATEGY AND SELECTION CRITERIA

Papers were identified by searching Medline and Pubmed using the terms “primary dystonia”, “secondary dystonia”, “idiopathic torsional dystonia”, “psychopathology”, “depression”, “anxiety”, “OCD”. Only papers published in English between 1990 and 2002 were included.

CORRESPONDENCE TO

A McNeill, 11 Broomieknowe Park, Bonnyrigg, Midlothian, United Kingdom. EH19 2JB. Tel: 0131-663-7485. E.mail: s9809172@sms.ed.ac.uk

USEFUL WEB SITES

http://www.dystonia.org - The U.K's only nation wide charity for dystonia sufferer's. Provides useful general information for patients and gives links to more advanced data for clinicians.

http://www.wemove.org

http://www.dystonia-foundation.org

http://www.neuroconsult.co.uk

References

6. Duffey PO, Butler AG, Hawthorne MR, Barnes MO. The
Aetiology of Co-morbid Psychiatric Disorders In Dystonia: A Biopsychosocial Hypothesis

38. Bruce ML. Psychosocial Risk Factors For Depressive Disorders In Late Life. Biol Psychiatr 2002; 52: 175 - 184.
Author Information
Alisdair McNeill, BscMedSci (Hons)
Medical Student, University of Edinburgh College of Medicine, Edinburgh University