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Review article

Mild parkinsonian features in dystonia: Literature review, mechanisms and clinical perspectives

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ABSTRACT

Dystonia is a hyperkinetic movement disorder that can be highly stigmatizing and disabling. Substantial evidence from animal models, neuropathological, neurophysiological, neuroimaging and clinical studies emphasizes the role of dopaminergic dysfunction in the pathophysiology of dystonia, illustrating possible pathophysiological overlap with parkinsonism. Furthermore, basal ganglia dysfunction has been implicated in the pathogenesis of dystonia, and is well established to underlie the manifestations of Parkinson's disease. Clinically, parkinsonian features are a key characteristic of some combined dystonias, including dopa-responsive dystonia, and Parkinson's disease often presents with dystonia. Moreover, many treatments effective in Parkinson's disease, both medical and surgical, also offer some benefit in dystonia. Therefore, mild parkinsonian features might logically accompany idiopathic and inherited isolated dystonias. However, as the current literature is particularly scant, the present review aimed to investigate mild parkinsonism in idiopathic and inherited dystonia. We found limited evidence alluding to the presence of mildly reduced arm-swing, increased tone, and non-decremental bradykinesia in adult-onset focal dystonia. Tremor, with postures, action and rest, also occurs commonly in idiopathic isolated dystonia, and can simulate Parkinson's disease tremor and be a cause of 'scans without evidence of dopaminergic deficit'. Parkinsonian features in monogenic isolated dystonias have been less well investigated, despite the potential benefit of correlating pathophysiological and clinical findings. The recognition and improved clinical characterization of parkinsonian features in idiopathic and inherited isolated dystonia extends the clinical spectrum of motor features in dystonia, which may help avoid incorrect diagnosis and inform therapeutic research.

1. Introduction

Dystonia is a hyperkinetic movement disorder characterised by involuntary sustained or intermittent muscle contractions, causing abnormal, often repetitive movements and/or postures [1]. Dystonic movements are characteristically patterned, twisting and may be tremulous, are often initiated or exacerbated by voluntary movements, and are frequently associated with overflow muscle activation [1]. Although uncommon, occurring in approximately 16 per 100,000 persons [2], dystonia is a highly visible and stigmatizing condition that adversely affects quality of life and can cause considerable morbidity [3,4]. Dystonia may be classified as inherited, acquired or idiopathic, the latter of which encompasses most adult onset focal or segmental dystonias [1], such as cervical dystonia, blepharospasm, oromandibular dystonia, laryngeal dystonia, and writer's cramp [5]. Multiple lines of evidence from neuroimaging studies, animal models of monogenic dystonias, and clinical evidence from combined dystonias point to the role of dopaminergic dysfunction and disturbed neural circuitry involving the basal ganglia, thalamus, cerebellum, and sensorimotor cortex in dystonia. Furthermore, basal ganglia diseases are well recognized to cause rigidity, bradykinesia, tremor, gait disturbance, loss of arm swing and facial hypomimia [6]. Consequently, there is good reason to expect that mild parkinsonian signs might accompany 'isolated' inherited and idiopathic dystonias. However despite this, there remains a surprising paucity of information characterizing the frequency of parkinsonian features in dystonia, and dystonia is often misdiagnosed [7,8]. Furthermore, treatment for dystonia

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remains symptomatic and largely empirical. Improved description of parkinsonian features in dystonia may facilitate a better understanding of the neural circuitry underpinning dystonia, assist in diagnosis, confer prognostic information, and assist in research regarding treatment. It is important to accurately distinguish between dystonia and Parkinson's disease as prognosis and treatment differs greatly. The present review therefore aims to explore the frequency and pathophysiological basis of parkinsonian signs in dystonia. The hallmark of Parkinson's disease is decremental bradykinesia, which is defined in the UK Brain Bank Criteria as "slowness of initiation with progressive reduction in speed and amplitude of repetitive action" [9]. Non-decremental bradykinesia, the occurrence of a 'null-point' and the absence of re-emergent may be useful features in differentiating mild parkinsonism in dystonia from true parkinsonism.

2. Pathophysiological basis for parkinsonian features in dystonia - the role of dopaminergic dysfunction

A broad range of evidence from animal models, neuropathology, neuroimaging, neurophysiology, and clinical studies of inherited dystonia, idiopathic dystonia and drug-induced dystonia foregrounds the role of dopaminergic dysfunction and disturbed basal ganglia circuitry in dystonia. Animal models have been of great value in elucidating the pathophysiology of dystonia. Abnormal basal ganglia circuitry, namely an imbalance in direct and indirect pathways, has been hypothesized to reduce motor inhibition in dystonia, leading to excessive muscle contractions [6,10]. For instance, increased dopamine turnover [11,12], impaired dynamic dopamine release [13], and failed physiological inhibition of striatal GABA release in response to administration of quinpirole, a D2-like receptor agonist [14] have been demonstrated in *DYT1* models, highlighting the role of basal ganglia and dopaminergic dysfunction. Additionally, other models highlight possible mechanistic overlap between dystonia and parkinsonism. For instance, in a baboon model, complete destruction of dopaminergic neurons with 1-methyl-4-phenyl-1,2 3,6-tetrahydropyridine (MPTP) caused a transient dystonia followed by hemiparkinsonism [15]. The dystonic phase correlated with decreased striatal dopamine content and a transient decrease in D2-like receptor number [15]. In contrast, partial striatal dopamine depletion followed by weakening of the orbicularis oculi muscle has led to blepharospasm [16], suggesting that dopamine depletion may predispose to dystonia, but that other factors are required for its development. These models indicate defective striatal dopamine handling, predominantly resulting in dopamine deficiency, may predispose to dystonia. It is also well recognized that striatal dopamine deficiency is responsible for the cardinal motor features of Parkinson's disease, and therefore plausible that mild striatal dopamine deficiency in dystonia might produce mild parkinsonian signs.

Limited neuropathological evidence indicates dopaminergic transmission is altered in dystonia and highlights mechanistic overlap between dystonia and parkinsonism. In examining striatal tissue from four DYT1 cases, including three typical DYT1 cases and one parkinsonian case, and six controls, higher 3,4-dihydroxyphenylacetic acid (DOPAC)/dopamine ratios were observed in dystonia compared to controls [17]. This indicates increased dopamine turnover, consistent with DYT1 animal models. In contrast, the parkinsonian case exhibited markedly reduced striatal dopamine, DOPAC and homovanillic acid, and loss of pigmented dopaminergic neurons in the substantia nigra, however without Lewy bodies or mutations in the *parkin* gene. Similar to animal models, *DYT1* mutations may predispose to dystonia and parkinsonism, leaving other factors to dictate the eventual phenotypic expression. Interestingly, torsinA (DYT1) associates with α-synuclein in Lewy bodies in human brain tissue [18], however neither the *DYT1* gene, nor any other genes involved in monogenic dystonia, have been shown to modify the risk of developing Parkinson's disease in genome-wide association studies [19,20].

Additionally, DYT3 (Lubag) is an X-linked dystonia-parkinsonism: it often presents with focal dystonia, and parkinsonism develops later [21]. Neuropathology of those with DYT3 has demonstrated predominant loss of striatal projection neurons in striosomes and patchy loss in the surrounding matrix in dystonics, and more widespread striatal neuronal loss encompassing the matrix in those with parkinsonism [22]. Similarly, rapid-onset dystonia-parkinsonism (DYT12) is characterised by the abrupt onset of dystonia and parkinsonism, often following a period of stress [23]. Neuropathological examination of four individuals with DYT12 identified degeneration in the basal ganglia and cerebellar pathways [24]. Although the majority of patients with idiopathic or inherited dystonias possess no neurodegeneration, these studies illustrate that it is possible the pathophysiology of those with dystonia and mild parkinsonian signs differs from those with purely dystonia. It is conceivable this may influence their response to therapies such as levodopa and anticholinergics, and therefore measurement of mild parkinsonian signs in therapeutic studies of dystonia may be helpful.

Substantial neuroimaging research further implicates dopaminergic and basal ganglia dysfunction in dystonia. Reduced striatal uptake of uptake of D2-like radioligands has been consistently associated with symptomatic writer's cramp [25], spasmodic dysphonia [26], nearly asymptomatic cervical dystonia [27], and nonmanifesting *DYT1* [28,29] and *DYT6* carriers [29]. Reinforcing evidence from animal models and human neuropathology, this suggests dopaminergic deficit may predispose to dystonia, but that other factors are required for its manifestation. However, only one imaging study of ten patients with writer's cramp assessed parkinsonian features, demonstrating that they did not have bradykinesia using a pegboard test, and that hypokinesia, rigidity and resting tremor were absent in these patients [30]. Therefore, although neuroimaging has implicated dopaminergic dysfunction in dystonia, further research is needed to clarify to what extent neuroimaging abnormalities correlate with the clinical features of dystonia.

Additionally, both neurophysiological similarities and differences exist between dystonia and Parkinson's disease. A novel study compared patterns of cortical synchronization in 22 patients with isolated cervical or segmental dystonia against 14 patients with akinetic-rigid Parkinson's disease, observing increased phase-amplitude coupling in the primary motor cortex and premotor regions compared to the primary sensory cortex in both dystonia and Parkinson's disease groups, and a reduction of this in both groups in response to therapeutic deep brain stimulation (DBS) [31]. Phase-amplitude coupling, a physiologic phenomenon important for information processing between and within cortical regions, has been related to the expression of parkinsonism [32,33]. In contrast, a study compared globus pallidus internus (GPi) neuronal activity in 29 patients with advanced Parkinson's disease and 13 patients with primary dystonia. They found marked differences the activity of GPi neurons in dystonia compared Parkinson's disease, across both linear (e.g. reduced firing rates and increased burstiness in dystonia) and non-linear (e.g. lower entropy and temporal organization of firing in dystonia) parameters [34]. Therefore, although Parkinson's disease and dystonia are distinguishable neurophysiologically, there is sufficient overlap to support a neurophysiological basis for parkinsonian signs in dystonia.

A small body of evidence raises the possibility that genetic factors in idiopathic dystonia may be associated with parkinsonian

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