Postural instability and falls in Parkinson's disease

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Abstract: Postural instability (PI) is one of the most debilitating motor symptoms of Parkinson's disease (PD), as it is associated with an increased risk of falls and subsequent medical complications (e.g. fractures), fear of falling, decreased mobility, self-restricted physical activity, social isolation, and decreased quality of life. The pathophysiological mechanisms underlying PI in PD remain elusive. This short review provides a critical summary of the literature on PI in PD, covering the clinical features, the neural and cognitive substrates, and the effects of dopaminergic medications and deep brain stimulation. The delayed effect of dopaminergic medication combined with the success of extrastriatal deep brain stimulation suggests that PI involves neurotransmitter systems other than dopamine and brain regions extending beyond the basal ganglia, further challenging the traditional view of PD as a predominantly single-system neurodegenerative disease.

Keywords: deep brain stimulation (DBS); dopamine; extrastriatal system; falls; Parkinson's disease; postural instability.

Introduction: postural instability

Postural instability (PI) is one of the common symptoms of Parkinson's disease (PD). PI also leads to falls in many PD patients and, often, injuries (Koller et al., 1989). In this short review, our aim is to provide a critical appraisal of the literature on PI in PD, including the clinical features, the neural and cognitive substrates, and the effects of dopaminergic medications and deep brain stimulation (DBS).

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Clinical features

PI is one of the most debilitating motor symptoms of PD. It usually develops at Hoehn and Yahr stage III and is relatively rare in early-stage PD (Grimbergen et al., 2009). PI is more common among PD patients with rapid disease progression (Jankovic et al., 1990), as well as in advanced rather than early stages of PD (Kim et al., 2013). PI is known to cause falls in many patients (Koller et al., 1989). Along with other contributing factors, including gait disturbance and dyskinesias, PI places patients at a high risk for intrinsic falls (Bloem et al., 2001). Previous accounts, both retrospective and prospective, report that the percentage of PD patients who fall ranges from 38% to 68% (Gray and Hildebrand, 2000; Ashburn et al., 2001; Balash et al., 2005; Michalowska et al., 2005; Allcock et al., 2009; Merola et al., 2011). Falls are associated with several sequelae, including fractures, 'fear of falling,' i.e. a fear of future falls (Rahman et al., 2011), decreased mobility, self-restriction of physical activity, social isolation, and decreased quality of life (Bloem et al., 2001; Bronte-Stewart et al., 2002; Adkin et al., 2003; Grimbergen et al., 2004; Michalowska et al., 2005; Cakit et al., 2007).

Assessment of PI in PD

Clinical documentation of PI in PD often relies on the retropulsion test (Postural Stability Item #30 of the Unified Parkinson's Disease Rating Scale), which involves a sudden backward pull of the shoulders (Grimbergen et al., 2004). Patients are considered to have PI if they take more than two steps backward or if they do not display an adequate postural response (Jankovic, 2008). This test, however, is difficult to standardize, and as such, the interpretation of its results is considerably arbitrary (Bloem et al., 1996; Chong et al., 2011). Findings of worsened PI in

conditions of limited sensory and proprioceptive feedback have also led to questions regarding the ecological validity of this test when used in the clinical setting (Bronte-Stewart et al., 2002; Shivitz et al., 2006). Additionally, the findings of quantitative subclinical aspects of PI in early stages of PD has led some researchers to question the sensitivity of current clinical methods of assessment, which may otherwise classify only those advanced-stage patients with more obvious signs of PI (Chastan et al., 2008; McVey et al., 2009; Geurts et al., 2011). Quantitative assessment of aspects of PI in PD generally relies on posturography, an electrophysiological assessment of human balance (Grimbergen et al., 2009). Static posturography determines the position of different body parts relative to one another in quiet stance (Visser et al., 2008), while dynamic posturography measures postural reactions to experimentally induced perturbations to balance, often using multidirectional shifting force plates (Horak et al., 2005; King and Horak, 2008; Visser et al., 2008).

PD patients may display clinical features of PI that are evident during quiet, undisturbed stance, such as poor anticipatory postural responses, abnormal postural sway, and inadequately organized automatic postural reactions. Performing voluntary actions, such as leaning, may reveal reduced limits of stability. Additional deficits may be evident upon disequilibrium, including slower compensatory stepping reactions, direction-specific instability, and incorrectly directed protective arm movements (Horak et al., 2005; Mancini et al., 2008; Grimbergen et al., 2009; Rocchi et al., 2012).

Neural substrates

Recent findings of more extensive grey matter degeneration in PD patients with PI than in PD patients without PI (Rosenberg-Katz et al., 2013), as well as the inconsistent effects of dopaminergic therapy on PI in PD (as discussed below), have led some researchers to suggest that the postural and balance deficits in PD may result from lesions to both dopaminergic and nondopaminergic nuclei (Bloem et al., 1996; Rocchi et al., 2002; Grimbergen et al., 2009). Some hypotheses involve noradrenergic deficiencies in the locus coeruleus (Grimbergen et al., 2009) and cholinergic and glutaminergic deficiencies in the pedunculopontine nucleus (PPN) (Bloem et al., 2004; Muller and Bohnen, 2013).

The body of literature in support of the involvement of neurotransmitters other than dopamine in deficits in postural stability is increasing (e.g. Putzki et al., 2002; Ondo and Hunter, 2003). Acetylcholine is one such neurotransmitter that has been implicated in the occurrence of PI (Muller and Bohnen, 2013). The PPN, a structure of the mesencephalic reticular formation, which forms the key cholinergic input to the thalamus, has been proposed to play a key role in the maintenance of balance (Welter et al., 2015). This proposed role follows findings of PPN degeneration occurring in PD (Bohnen et al., 2009), an association between cholinergic hypofunction in the PPN and falls in PD (Bohnen et al., 2009), balance deficits induced in healthy monkeys by selective cholinergic PPN lesions, and correlations between PPN cholinergic loss (rather than nigrostriatal loss) and balance deficits, both in the Parkinsonian state and in neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-treated aging monkeys (rather than young monkeys) (Karachi et al., 2010). *In vivo* acetylcholine positron emission tomography imaging has added additional support, with findings of PD fallers having significantly decreased thalamic cholinergic innervation compared with PD nonfallers, while not significantly differing in the degree of dopaminergic denervation (Bohnen et al., 2009, 2012). A mechanistic explanation provided by Sarter et al. (2014) posits that impaired cholinergic transmission might impinge on the attentional control of posture and detection of movement errors, limiting attentional stabilizing compensatory mechanisms to a balance perturbation, increasing the likelihood of a fall.

The effects of dopaminergic medications and DBS

The pathophysiology of PI in PD is not well understood. A number of studies examining dopaminergic intervention have found that current medications often have a refractory effect on PI, similar to that of the other axial symptoms of the disease (Rocchi et al., 2002; Lord et al., 2014). Additionally, it has been suggested that dopaminergic medication might actually contribute to the incidence of falls, as the amelioration of dopa-responsive symptoms (e.g. bradykinesia and rigidity) improves and promotes active mobility, while the underlying balance disorder remains untreated. This might be due to other systems' underlying control of posture and balance (e.g. set-dependent flexibility, sensory integration, and postural synergies) being associated with neural circuits with lower sensitivity to levodopa, as well as DBS, as will be discussed later (Horak et al., 1996; Chong et al., 2000; Bloem et al., 2001; Bronte-Stewart et al., 2002; Rocchi et al., 2002; Grimbergen et al., 2004; Shivitz et al., 2006; Lyoo et al., 2007).

Levodopa-induced dyskinesias have also been suggested to act as an independent factor that aggravates PI in patients with advanced PD (Armand et al., 2009). However, some postural abnormalities have been found to be at least partially dopa-responsive, albeit often not being improved to normal levels (Beckley et al., 1995; Rocchi et al., 2012).

Some research has attempted to ameliorate deficits in postural stability with nondopaminergic medications. Putzki et al. (2002) compared the N-methyl-D-aspartate (NMDA) antagonist Flupirtine with placebo, finding a nonspecific improvement of overall UPDRS scores in placebo and Flupirtine conditions compared to baseline measures (more marked in the placebo condition) and no improvement in the motor subscale. In a randomized crossover study, Chung et al. (2010) found that by enhancing cholinergic transmission with the cholinesterase inhibitor Donepezil in PD patients, rates of falling were reduced by approximately half when compared to a placebo condition. Larger trials investigating the impact of cholinergic augmentation on postural stability and balance are recommended.

Stereotactic functional neurosurgery has also been studied as a possible treatment for PI in PD. The results of some studies investigating the effect of DBS of the globus pallidus internus (GPi) have been moderate (Lyons et al., 2002; Volkmann et al., 2004; Rodriguez-Oroz et al., 2005). Several authors have found initial improvements in balance and aspects of PI (as measured by PIGD scores) not being sustained in the long-term while in the OFF medication state, but being sustained when using dopaminergic medication (for a review, see St. George et al., 2010). This initial improvement might be attributable to amelioration of cardinal symptoms such as rigidity and bradykinesia that constrain posture (St. George et al., 2010).

DBS of the subthalamic nucleus (STN) has shown some clinical value in alleviating some aspects of PI, for example improving postural sway (Rocchi et al., 2002). A 5-year follow-up study following bilateral STN-DBS found that ON-medication PI worsened over time, but it improved when OFF-medication (Gervais-Bernard et al., 2009). Sidiropoulos et al. (2013) compared the long-term effects of high- and low-frequency STN-DBS and reported no significant improvements of balance. Yamada et al. (2008) found that axial features that were unresponsive to levodopa (e.g. freezing, gait, posture, and PI) were ameliorated by STN-DBS only when the features were mild, suggesting the need to identify alternative target structures involved in axial functions that are not reliant on dopaminergic systems.

St. George and colleagues (2010) conducted a meta-regression of the long-term effects of DBS on PD motor symptoms. They concluded that STN-DBS and GPi-DBS provide greater relief from the cardinal symptoms of PD, than to posture and gait, postulating that axial and distal control are differentially affected by DBS. Recent research, however, has shown that a relatively new target for DBS, the PPN, appears promising in ameliorating balance and postural deficits.

Low-frequency stimulation of the PPN in advanced PD patients has been found to improve aspects of PI (Plaha and Gill, 2005; Stefani et al., 2007; Moro et al., 2010). The low stimulation frequencies used for PPN stimulation mean that the battery life of the pacemaker could be extended, potentially providing a cost-effective treatment that could even be viable in developing nations (Kringelbach et al., 2007). Bejjani et al. (2000) have suggested that the observed synergistic effect of levodopa and STN-DBS improving PI might operate by modulating the nondopaminergic descending STN-PPN pathway. Another synergistic effect observed between STN-DBS and PPN-DBS has shown greater efficacy in improving PI than either target alone, as found in one study (Tykocki et al., 2011).

An understanding of the mechanisms of PPN-DBS remains relatively elusive, but it has been suggested that it might include modulation of either ascending and/or descending projections or modulation of the proximally located lemniscal system (Moro et al., 2010). Future research evaluating PPN-DBS should include a greater number of patients, double-blinded designs, longer-follow up, and objective measures of PI and gait (Mancini et al., 2011; Nonnekes et al., 2015) to confirm the outcome of early preliminary reports.

Cognitive correlates

There is a growing literature in support of the role of cognitive processes in the maintenance of balance and posture in healthy humans, as well as the role of cognitive dysfunction in PI in PD (Borel and Alescio-Lautier, 2014). Deficits on several cognitive tests correlated with PI and falls, including the Mini-Mental State Examination, tests of word learning, and the Frontal Assessment Battery (Lee et al., 2012; Paul et al., 2014). As will be noted below, attentional dysfunction appears to play an important role in postural and balance issues, as not only do PD patients have attentional deficits in comparison to healthy controls, PD patients with PI have been observed to also have greater deficits compared to PD patients who do not exhibit PI (Allcock et al., 2009).

Several authors have investigated the relationship between PI and falls within the two phenotypic subtypes of PD: tremor-dominant and PI/gait difficulty (PIGD), as delineated by Jankovic et al. (1990). Belonging to this PIGD group, as well as a progression from the tremor-dominant type to PIGD subtype, has been demonstrated to relate to a higher risk of cognitive decline (Alves et al., 2006; Burn et al., 2006; Nocera et al., 2010; Domellof et al., 2011). PD-PIGD patients, when compared with PD-tremor-dominant patients, have greater impairment on measures of global cognition (Verbaan et al., 2007) and a higher frequency of PD with mild cognitive impairment (PD-MCI) diagnoses (Poletti et al., 2012). In those PD-MCI patients, symptoms of PIGD are more severe than in cognitively intact PD patients (Williams-Gray et al., 2007). Notably, PIGD is also associated with an increased risk of developing dementia (Wood et al., 2002; Williams-Gray et al., 2007; Camicioli and Majumdar, 2010), with some authors implicating cholinergic pathways in the pathology of dementia in PD (Whitehouse et al., 1983; Perry et al., 1985; Hilker et al., 2005; Gratwicke et al., 2015).

Specific associations between cognitive domains and component PIGD items have been found, suggesting that the relationship between cognition and PIGD is multifaceted (Kelly et al., 2015). Executive dysfunction (specifically processing speed) was found to be associated with more severe impairment in all component PIGD items (gait, freezing of gait, and PI), whereas poorer memory function was only associated with PI (Kelly et al., 2015).

Some researchers suggest common pathways connecting increasing postural and gait impairments and cognitive decline, one in which acetylcholine is implicated (Nocera et al., 2010; Yarnall et al., 2011). However, the findings of complex patterns of association between distinct aspects of PIGD and specific cognitive domains brings to light that multiple neural relationships might be involved in the association between cognition and posture and gait control (Kelly et al., 2015). There is a growing understanding of the anatomical connectivity between nuclei involved in gait, such as the PPN, and other regions like the basal ganglia and frontal cortex (Mena-Segovia et al., 2004; Nocera et al., 2010).

Dual-task experiments, in which a participant is required to carry out a primary gait or postural task as well as a secondary cognitive task, have been important in highlighting the interaction between cognition and posturomotor deficits (Yarnall et al., 2011). An increase in stride-to-stride variability, which is associated with a significantly increased risk for falls, is seen in PD patients during dual-tasking (Schaafsma et al., 2003; Yarnall et al., 2011). The introduction of a concurrent task, including color judgment (Ashburn et al., 2001), reading and monologuing (Holmes et al., 2010), sequential finger movements, arithmetic calculation (Marchese et al., 2003), and visuospatial tasks (Schmit et al., 2006), has been found each to result in significantly greater PI in those with PD when compared with age-matched controls.

Similar to the symptom of freezing of gait in PD (Shine et al., 2013), PI is associated with deficits in cognitive processes, with attention appearing to be particularly important. In light of the mechanistic explanation provided by Sarter et al. (2014), it makes sense that attentional dysfunction is associated with PI, as impairments in transmission of acetylcholine related to PPN damage can affect attentional control over posture and the detection of movement and balance errors, which can then lead to falls.

Conclusions

PI in PD is a complex and apparently multifactorial phenomenon, presenting a challenge for current treatment. As has been demonstrated by a number of studies, a proportion of falls in PD are the result of an intrinsic, underlying balance disorder and not merely the result of environmental obstructions. The difficulty in predicting which patients with PIGD deficits are more at risk of falling, alongside the resultant psychological, physical, and social consequences of a fall in advanced PD, makes obvious the necessity of further understanding the pathophysiology of this symptom and potential strategies for its treatment.

Such future research should continue to examine the contribution of both dopaminergic and nondopaminergic systems to balance and posture (Lord et al., 2014). Evidence of the PPN's involvement in posture and balance, as well as its anatomically high interconnectedness with the basal ganglia, makes this structure one such candidate for further physiological and treatment-oriented exploration. Along this line of thinking, the development of neuroimaging techniques that can assess the structural, anatomical, and functional integrity of nondopaminergic systems is essential, if we are to glean understanding of their contribution to PI (Grimbergen et al., 2009). One such neurotransmitter system that appears to be important and necessitating further inquiry is acetylcholine, as there is mounting evidence of associations between cholinergic pathways and PIGD deficits, cognitive dysfunction, and the development of dementia in PD. Some researchers suggest a shared neural pathway between increasing PIGD impairment and cognitive decline (Nocera et al., 2010).

Investigation of alternative pharmacological treatments, for example those that act on cholinergic or GABAergic systems, is recommended, as dopaminergic medication has been repeatedly reported to not effectively alleviate PI in PD and to sometimes even aggravate the symptom. In addition, laboratory findings of subclinical aspects of PI in early PD suggest that the clinical assessments currently utilized are not sensitive enough in their detection of PIGD dysfunction. As well as remedying this lack of sensitivity and improving predictability for future falls, the development of more stringent PIGD assessments (beyond the UPDRS) could be used to both monitor the progression of PI in PD and further investigate the relationship between specific cognitive functions and particular aspects of postural control (Nocera et al., 2010). It is imperative that future pharmacological and nonpharmacological treatment is informed by comprehensive and multidisciplinary research teams, involving neurologists and psychologists and other allied health professionals, to ensure that patient care encompasses treating both motor and nonmotor disease features and, importantly, is individually tailored.

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