CHAPTER 2: PARKINSON'S DISEASE AND ITS DEMENTIA: PATHOLOGY AND CONSIDERATIONS IN POSTURAL CONTROL

Parkinson's Disease

Epidemiology and Clinical Characteristics

PD is the second most common neurodegenerative disorder, behind AD. The incidence of PD varies according to age group, with some estimates placing the incidence rate at a median of 14 per 100,000 person years in developed countries. When restricted to ages 65 and above, the incidence increases dramatically to 160 per 100,000 person-years. Based on American and European data, the prevalence of PD among people 65 years or older has been estimated at 950 per 100,000 (Hirtz et al., 2007).

Patients classically present with a resting tremor, rigidity, bradykinesia, gait impairment and postural instability, which are known as the "cardinal features" of PD. It is a progressive illness and motor symptoms usually present unilaterally with gradual progression to involve the other side of the body. Also present are any number of non-motor symptoms (NMS) including postural instability, autonomic dysfunction (i.e. orthostatic hypotension, gastrointestinal (GI) disturbances), mood disorders, sleep disturbances, speech difficulties and dementia. These NMS are also referred to as non-dopaminergic symptoms as most are refractory to dopamine replacement therapy (DRT) (Olanow & Schapira, 2012). As gait dysfunction and postural instability are important in the consideration of falls in PD, they are discussed in greater detail below.

Falls

Prospective studies have estimated that around two-thirds of patients with PD will experience at least one fall per year (Wood, Bilclough, Bowron, & Walker, 2002). Indeed, a recent systematic review found that an average of 60.5% of PD patients have fallen at least once and that 29% of falls are recurrent (Allen, Schwarzel, & Canning,

2013). Fall-risk is a complex matter which is individual to each patient and their circumstances, making prediction of falls a difficult task. Proposed risk factors for falls include freezing of gait, "stooped" posture, cognitive dysfunction, balance control problems and muscle weakness in the legs (Latt, Lord, Morris, & Fung, 2009). The National Parkinson Foundation's Falls Task Force has recently developed a summary of generic and PD-specific fall risk factors, with the single most important risk factor being a personal history of previous falls (van der Marck et al., 2014). A summary of these risk factors as described by Fasano and colleagues (Fasano, Canning, Hausdorff, Lord, & Rochester, 2017) can be found in Table 1 below.

Table 1: Generic (age-related) and PD-specific fall risk factors identified by the Falls Task Force promoted by the National Parkinson Foundation

Generic	**Specific (PD-related)**
Anxiety	Axial rigidity
Arthrosis	Cognitive (frontal) impairment
Cardiac arrhythmia	Disease severity
Daily use of alcohol	Dual tasking
Depression	Dyskinesias
Environmental hazards	Fall history
Female gender	Freezing of gait and festination
Old age	Functional neurosurgery (particularly STN DBS)
Orthostatic hypotension	Higher total doses of levodopa
Osteoporosis	Use of dopamine agonists, anticholinergic
Other comorbidities (vertigo, peripheral neuropathy)	Postural abnormalities

Polypharmacy (use of > 3 drugs other than anti-PD) Sedative drugs, particular (multiple) benzodiazepines Use of an assistive device Visual and ocular motor impairment Weakness due to inactivity	Postural instability Shuffling and small scaled gait Slow mobility Transfers Urinary incontinence

Note. Reprinted from "Falls in Parkinson's Disease: A Complex and Evolving Picture" by Fasano, A. et al., 2017, *Movement Disorders*, *32(11),* p.1525.

A prospective investigation of the direct causes of falls in PD determined that 31% of falls were sudden falls, 20% were due to freezing and festination, 12% each were due to neurologic and sensory disruptions or environmental factors, respectively, 11% were contributed to postural instability, 4% were secondary to orthostatic hypotension and 3.6% were a result of severe dyskinesia (Rudzińska et al., 2013). As intrinsic causative factors were dominant in this study, there exists a basis for pharmacologic intervention especially considering that 23% of falls were contributed to neurologic deficits and postural instability – two factors that may be ameliorated with cholinergic therapy. This will be discussed in further detail in the section entitled "*Drugs Affecting Cholinergic Neurotransmission."*

Gait Dysfunction

Common gait abnormalities in PD include a slowed gait velocity, a decreased stride length manifesting as a shuffling gait, festination and a freezing of gait where the patient experiences a momentarily block and is unable to initiate or continue forward gait. Freezing of gait is a phenomenon where patients seem unable to lift their feet from the ground and typically occurs upon initiation of gait, when a patient attempts to initiate a

turn or when adjusting their step. This freezing may occur spontaneously as the disease progresses and often leads to falls (Giladi et al., 2001).

Freezing of gait and falls are closely linked in PD, perhaps because both are relatively common in later stages of the illness and less common in *de novo* Parkinson's. Both conditions are also unresponsive to DRT and may even exhibit a paradoxical worsening with therapy. Therefore, it is hypothesized that the two may be interrelated and share a non-dopaminergic origin (Bloem, Hausdorff, Visser, & Giladi, 2004).

Another observation is that PD patients may exhibit a decreased braking capacity. In normal subjects, the CoM tends to fall during the swing limb period; however, the subject is able to brake and reverse the fall before foot contact. In PD patients, both step length and velocity are reduced which may result in a marked reduction in braking capacity and an increase in postural instability during gait. This is thought to be a result of both dopaminergic and non-dopaminergic lesions. The above was demonstrated in a study conducted by Chastan and colleagues that compared 32 normal controls to 32 patients with PD. In the PD group, dopamine replacement therapy improved gait in all and braking capacity in 7 of 32 patients, however, those with impaired braking capacity also had a small N-mesencephalon surface area compared to PD patients with normal braking capacity (Chastan et al., 2009). The PPN is a cholinergic structure of the mesencephalon and as mentioned previously, it is hypothesized to play a crucial role in gait initiation and postural control. The role of the PPN in PD will be discussed further in the following section.

Postural Instability

Postural instability is considered one of the cardinal features of PD, presenting late in the course of illness. Along with other axial symptoms, it is a major determinant of disability and poor quality of life in patients with PD (Muslimovi et al., 2008). As a result of this instability, patients tend to fall more frequently and also display a debilitating fear of falling, contributing significantly to disease morbidity (Adkin, Frank, & Jog, 2003).

Postural instability manifests as a progressive loss of postural reflexes, however the underlying pathophysiologic mechanisms are complex, involving both the underlying disease process and compensatory mechanisms, and are poorly understood (Benatru et al., 2008). Patients with PD also have a "stooped" posture, essentially pushing the foot CoP forward, and is an independent risk factor for falls (Latt et al., 2009). However, it is unknown whether this posture is compensatory or causal (Kim et al., 2013).

Postural instability is often measured either through clinical balance tests or using static or dynamic computerized posturography. Computerized posturography measures the foot CoP and other sway paramaters including its mean velocity and area of displacement. The mean velocities of CoP displacement and the total area of CoP displacement are validated measures of fall risk (J. E. Visser et al., 2008). However, the measurement of balance using static computerized posturography in PD has yielded conflicting results, with some showing increased or normal (Schieppati & Nardone, 1991) and even reduced postural sway (F. Horak, Nutt, & Nashner, 1992). It is likely that the heterogeneity of PD and its treatment as well as the variations in study design are contributing to the variation in these observations.

Alterations in Postural Reflexes

Patients with PD display abnormal APAs and APRs and the type of abnormality may depend on the stage of illness. In early PD, patients exhibit exaggerated APAs as shown by Inkster and colleagues. In their study, patients with PD tended to overuse hip strategies to place the CoM excessively forward in preparing to stand from a chair. Conversely, patients in the more advanced stages tend to have diminished APAs (Bleuse et al., 2008). Bleuse and colleagues demonstrated that PD patients in the "OFF" phase displayed reduced APA magnitude compared to normal controls. Patients were required to stand on a force platform and perform a right shoulder flexion movement to grasp a handle in front of them under various conditions. Patients with PD showed a reduced magnitude of their APAs as the maximal velocity peak of the CoP appeared later and the amplitude of the CoP backward displacement was lower.

With respect to APRs, PD patients exhibit decreased trunk rotation and ankle torque changes in response to support surface rotations, which suggests a stiffening response to postural perturbations (Carpenter, Allum, Honegger, Adkin, & Bloem, 2004). Postural reflexes also show a disordered activation in PD as destabilizing (medium-latency stretch responses) stretch reflexes are increased, while stabilizing (long-latency stretch responses) stretch reflexes are unaffected or lessened (Carpenter et al., 2004; Kim et al., 2013). The distal-proximal activation sequence of long-latency reflexes was also reversed following toes-up platform rotations in patients with advanced disease reflecting an inappropriate selection of motor programs and modulation of postural reflexes (Beckley, Bloem, Van Dijk, Roos, & Remler, 1991).

Patients also show a disability in adjusting to changes in postural demands such as the inability to suppress an initial postural response and adjust for a rapid change. PD patients have shown a reduced ability to suppress ankle muscle responses following rapidly changing translations in support surface. PD patients also display reduced suppression of both medium and long-latency postural reflexes when converting from a freestanding position to holding onto an object for support (F. Horak et al., 1992).

Pathophysiology of Abnormal Postural Reflexes

Dysfunction in the basal ganglia likely contributes, in part, to the disordered postural reflexes in PD. As the inhibitory capacity of the substantia nigra reticulata is reduced secondary to dopaminergic deficit, medium-latency reflex amplitudes are increased (Scholz et al., 1987), whereas the reversal in the sequence of long-latency reflexes represents disordered selection and initiation of motor programs (Beckley et al., 1991).

The supplementary motor area connects indirectly with the basal ganglia (described below) and studies have shown altered function of this area in PD (Cunnington et al., 1996). As this area is thought to be involved with the preparation of voluntary movement and more specifically APAs, this may provide a partial explanation for the aberrant

APAs, as described in the previous section, that are observed throughout the course of PD (Massion, 1992).

Pathophysiology of Parkinson's Disease

Pathologically, PD is characterized by hypofunction and loss of dopaminergic neurons in the substantia nigra pars compacta, reductions in striatal dopamine and Lewy body deposition (Olanow & Schapira, 2012). The substantia nigra pars compacta is one of two components of the substantia nigra. The substantia nigra forms part of the basal ganglia along with the striatum, globus pallidus and the subthalamic nucleus. The basal ganglia are a group of subcortical nuclei that play a critical role in regulating motor function (Olanow & Schapira, 2012).

The basal ganglia receive input from the cerebral cortex via the striatium, while the globus pallidus and substantia nigra pars reticulata (the other division of the substantia nigra) provide output to thalamocortical and brainstem motor regions. This output provides inhibition to thalamic and brainstem neurons that connect to motor areas of the cerebral cortex and spinal cord. The main role of the dopaminergic projections from the substantia nigra pars compacta is to modulate neuronal firing in the basal ganglia (Olanow & Schapira, 2012). Therefore, it can be seen how dysregulation (or denervation) in the substantia nigra pars compacta may result in decreased modulation or increased firing of output neurons in the basal ganglia. This results in increased inhibition of thalamic and brainstem neurons and subsequent reductions in the activation of cortical motor systems. This is what leads to the development of clinical parkinsonian symptoms (Olanow & Schapira, 2012).

While dopaminergic loss may explain the majority of motor symptoms in PD, neurologic dysfunction in PD is widespread involving many brain structures and neurotransmitter systems, including serotonergic and cholinergic systems (Olanow & Schapira, 2012). While dopaminergic dysfunction is an important consideration in PD and represents the major target of pharmacotherapy, the remaining discussion will focus mostly on non-

dopaminergic pathways and in particular, cholinergic dysfunction and its role in postural control.

Cholinergic Pathophysiology in Postural Instability

Studies have shown that projections from the parabrachial and raphe nuclei as well as the locus coeruleus innervate the vestibular network and support hypothesis of serotonergic and noradrenergic involvement, respectively (Balaban, 2002; Grimbergen, Langston, Roos, & Bloem, 2009). However, the role of ACh has been an area of intense study in PD and fall-risk.

As mentioned previously, the PPN is a major source of ACh in the central nervous system and cholinergic neurons of the PPN are hypothesized to play a crucial role in gait initiation and postural control (Karachi et al., 2010). Studies show significant degeneration of this region in PD as well as in the nBM, which provides cholinergic stimulation to the cerebral cortex. Deep brain stimulation to the PPN has also shown some promise in decreasing falls in PD (Moro et al., 2010) as well as improving daytime sleepiness and executive function (Fasano, Daniele, & Albanese, 2012), both of which may indirectly contribute to fall risk.

As well, PET imaging of AChE activity has shown that cortical cholinergic hypoactivity is greater in PD patients who have fallen versus those who have not (N. Bohnen et al., 2009). This same study also showed that reduced AChE activity in the thalamus is also associated with falls in PD even after controlling for motor symptoms. However, it may also be useful to compare PD to progressive supranuclear palsy, where falls are an early presenting feature. Again, PET imaging of AChE activity has shown widespread reductions in cholinergic activity across the cerebral cortex in PD and PSP as well as more severe hypoactivity in subcortical areas in PSP than in PD (Gilman et al., 2010). This suggests a subcortical contribution to falling. The severity of gait and balance disorders in the study by Gilman and colleagues was correlated with cholinergic deficits in the midbrain and cerebellum. As the PPN has significant connections with both of

these structures as well as the thalamus, these studies lend support to the critical role of the PPN in postural control.

Parkinson's Disease Dementia (PDD)

Epidemiology and Clinical Characteristics

Dementia is exponentially more common among sufferers of PD than it is amongst the general population with one prospective, population-based study estimating a six-fold greater risk (Aarsland et al., 2001). A meta-analysis of 27 studies estimated the mean prevalence of dementia in PD at 39.9% (Cummings, 1988), with more recent estimates hovering around 30% (Aarsland & Kurz, 2010). Various risk factors for dementia in PD have been identified including age, older age at onset of PD, as well as duration and severity of PD (Aarsland et al., 2001).

Clinically, patients with PDD display hallmark deficits in executive function, characterized by major deficiencies in attention and planning. Patients also experience significant visuospatial impairments and difficulties with verbal memory. However, an important distinction in PDD is that patients experience less memory decline than those with AD, but the above deficits are usually more profound. Another distinguishing feature is that cognitive symptoms typically fluctuate in PDD, whereas AD patients experience a slow but progressive decline (Bronnick, Emre, Lane, Tekin, & Aarsland, 2007).

Pathophysiology of PDD

Cognitive dysfunction in PD is likely multifactorial and related to a variety of factors including lesions in the subcortical nuclei and degeneration of subcortico-cortical pathways. Lewy body inclusions are found in both cortical and limbic structures. Patients with PD also frequently display AD tau pathologies in combination with these features, however Lewy body disease is more closely correlated with cognitive function than AD

pathology (Emre, 2003; Jellinger, 2006; Kövari et al., 2003). As mentioned previously, significant degeneration of the nBM occurs in PD, with autopsy studies showing more progressive loss in the presence of cognitive impairment (Jellinger, 2006). In fact, PET studies comparing PDD to AD have shown that cortical AChE activity (serving as a marker for cholinergic activity) is even more reduced in PDD than in AD even when controlling for dementia severity (N. I. Bohnen et al., 2003). Degeneration of the PPN may also play a role as it may be involved in the sleep-wake cycle, consciousness and arousal (Perry et al., 1999). Decreased cholinergic output from the PPN may cause attentional dysfunction and fluctuations in consciousness and alertness, hallmark features of PDD (Yarnall et al., 2011).

A PET study conducted by Hilker and colleagues compared the uptake of cholinergic and dopaminergic markers (N-[^{11}C]-methyl-4-piperidyl acetate (MP4A) and ^{18}F-fluorodopa (FDOPA), respectively) in PD patients with and without dementia to age-matched controls (Hilker et al., 2005). Striatal dopaminergic marker uptake was not different between PD and PDD. However, PDD patients showed more severe cholinergic deficits in several regions. The reduction in global cortical MP4A binding was quite severe in PDD (29.7%, $p < 0.001$ vs. controls), but less so in PD (10.7%, $p < 0.01$ vs. controls). Interestingly, the PDD group also showed lower parietal, frontal and temporo-parietal MP4A uptake rates.

Although important, ACh is unlikely to be the sole culprit in PDD. It must be mentioned that dopaminergic and noradrenergic pathways are likely involved, particularly in the case of executive dysfunction and attention (Emre, 2003). Serotonin may also play a role in visual hallucinations (Ballanger et al., 2010), underlining the widespread neurologic dysfunction observed in PD and PDD.

PDD and Postural Control

Fall-risk is increased in patients with dementia (Nutt, Marsden, & Thompson, 1993). As postural control is simultaneously a reflexive and cognitive process, patients with PDD

represent a special case in that they display both aberrant anticipatory and reactive postural adjustments as well as cognitive dysfunction (Kim et al., 2013). The integration and re-weighting of visual, vestibular and proprioceptive information required to maintain posture and balance may be significantly impaired in the presence of cognitive dysfunction (F. B. Horak, 2006).

The most important aspect of this cognitive dysfunction is likely attention deficits, as this increases postural instability, as discussed previously, and as evidenced by the use of dual-task paradigms in both the elderly (Teasdale & Simoneau, 2001) and PD populations (Marchese, Bove, & Abbruzzese, 2003). As well, visuospatial deficits and decreased planning ability may respectively alter sensory perception and voluntary reactive strategies to maintain postural control.