Redefining Parkinson's Disease: More Than Just a Movement Disorder

Diana J. Kim, BSc, MSc, MD 2017, Pacific Parkinson's Research Centre, University of British Columbia

Traditionally, Parkinson's disease (PD) is characterized as a movement disorder consisting of tremor, rigidity, slow movements and postural instability – largely attributed to the progressive unexplained death of nigrostriatal dopaminergic cells. As the second most common neurodegenerative disorder after Alzheimer's disease, PD affects approximately 1 of 100 persons above the age of 60 years in industrialized countries,[1] and this prevalence rate escalates to as high as 4% with increasing age.[2,3] From disease diagnosis until death, PD progresses for a mean duration of 15 years.[4] Therefore, due to our growing elderly population, PD poses a significant burden on patients, families, the health care system and society.[1,5]

Typically, it is the emergence of the definitive cardinal motor symptoms that guides a patient into a neurologist's office.[6,7] Currently, we have an extensive understanding of how to manage motor symptoms effectively with levodopa medication, the gold standard for treating PD since its inception in the late 1960s.[8] However, by this time, greater than 50% of nigrostriatal fibres and 80% of striatal dopamine levels have already irreversibly deteriorated,[9,10] suggesting that the disease begins much earlier. This has resulted in a recent reclassification of PD to include a "premotor" phase.[11]

The importance of non-motor features in the treatment of PD is being increasingly recognized as non-motor features may present in the premotor phase, and, later on in the disease, may affect quality of life to a greater degree than normally-considered motor functions.[11,12] Motor deficits only comprise the "tip of the iceberg" with non-motor features – especially psychiatric – being far more numerous and equally insidious.[7,13] Yet, how do we improve the recognition and treatment of psychiatric symptoms in PD? Greater understanding of the psychiatric and behavioural symptoms of PD will advance and optimize disease assessment and management. This article briefly summarizes common neuropsychiatric symptoms in PD and elaborates on the associated challenges.

Neuropsychiatric Symptoms in PD

Common psychiatric disturbances observed in PD subjects include: depression, apathy (i.e., lack of motivation), anxiety, sleep disturbances, psychosis, cognitive impairment, and impulse control disorders, with at least one neuropsychiatric symptom being reported in over 60% of patients.[14-16] These symptoms may be either part of the disease pathophysiology and/or induced by treatment from dopaminergic medication.[17]

Corresponding Author:
Diana J. Kim
dianajykim@alumni.ubc.ca

Depression is one of the most common psychiatric symptoms in PD, reportedly seen in up to 72% of patients during first 10 years of the disease.[18] While it is tempting to speculate that depression may be triggered by an emotional reaction to having a disabling chronic illness, the disease itself in fact intrinsically underlies the pathophysiology. Both degeneration of serotonergic neurons and loss of limbic dopaminergic and noradrenergic innervation are associated with depression in PD.[17,19,20] While depression may appear at any stage of the disease, it may even precede the onset of motor symptoms by several years.[17,21,22] In support of this, individuals suffering from depressive disorder are associated with increased risks of later developing PD.[23] Furthermore, several clinical features of PD and depression overlap: altered appetite or sleep, weight change, loss of libido, memory impairment, low energy, lack of facial expression and psychomotor retardation.[12,15,21] As a consequence, signs of depression may sometimes be initially masked in PD.

Sleep disorders, such as insomnia, hypersomnia (excessive daytime sleepiness), restless leg syndrome and rapid eye movement sleep behaviour disorder (RBD), affect the majority of PD patients with prevalence rates as high as 60-98%.[17,24] Notably, about one third of PD patients suffer from RBD, which is characterized by loss of muscle atonia during REM sleep leading to subsequent physical enactment of dreams[14]. Similar to depression, RBD is a predictive factor for PD and also anticipates the later onset of motor symptoms. For example, one study demonstrated that 19-38% of RBD patients developed PD after 5 years.[25] RBD may be integral to the disease process since RBD precedes motor symptoms and involves dysregulation of brainstem nuclei. Although, as with many non-motor features in PD, it can be difficult to ascertain how much of the sleep problems in PD are due to the pathophysiology of PD itself or side effects of medication.[17]

Psychotic symptoms affect 20-40% of PD patients with the greater incidence being in older age and late onset PD.[24] Psychosis manifests as hallucinations (visual, auditory or tactile), paranoid delusions or delirium.[17] Up to 40% of patients experience benign visual hallucinations, which initially appear as non-threatening sensations in the visual field. With longer disease duration, however, hallucinations later become more stressful and disturbing for the daily lives of patients and caregivers.[14] The pathogenesis of psychotic symptoms arises from a complex interaction with many risk factors, such as older age, greater disease duration and severity, depression and cognitive impairment, RBD, autonomic impairment and poor visual acuity.[18,26] Intrinsic disease mechanisms may also contribute to the development of hallucinations; midbrain neurodegeneration, sleep dysfunction, or visual processing deficits are associated with subsequent occurrence of hallucinations in PD.[26] Exacerba-

tion of psychosis may be induced by dopaminergic medication, particularly dopamine agonists, therefore creating a challenge in symptom management.[27] Antiparkinsonian dopaminergic drugs tend to induce psychosis whereas antipsychotic drugs tend to worsen motor abilities.[17] Balancing the appropriate amounts of multiple medications is central in managing PD psychosis, and therefore atypical antipsychotics such as quetiapine are generally used.[28]

Individuals with PD have up to a six-fold greater risk of developing dementia compared to age-matched individuals without PD.[29] Cognitive impairment in PD is reflected in multiple core cognitive domains such as attention deficits, executive dysfunction, poor visuospatial and verbal memory and cognitive inflexibility.[30,31] About 25% of PD patients suffer from mild cognitive impairment, and 30% from dementia.[17,32] While dementia typically occurs later in the disease, the rate of cognitive decline is rapid after a stable period and critical inflexion point. In a sample of 238 PD patients, global cognitive abilities were assessed longitudinally by the mini-mental state examination (MMSE). MMSE scores were steady until about 13 years after PD diagnosis and thereafter, cognitive abilities declined annually by 2.8 points.[33] Nevertheless, the Montreal Cognitive Assessment (MoCA) has been suggested to be more sensitive than the MMSE for executive dysfunction and mild cognitive impairment seen in PD,[34] which may affect interpretation of MMSE decline.

Cognitive impairment in PD may be difficult to manage due to the heterogeneous clinical phenotypes. A possible reason for the heterogeneity may be due to the cell loss in dopaminergic, cholinergic and other neurotransmitter systems.[15] Advanced age, presence of psychosis, less robust response to levodopa are certain risk factors for developing dementia in PD; however, age of PD onset as well as disease duration are unrelated to cognitive impairment.[18,35] Therefore, dementia in PD is rather unpredictable when assessed relative to timeline of motor symptoms.

An increasingly recognized side effect of dopaminergic medication, particularly dopamine agonists, in PD is disruption of impulse control with a frequency of around 13-17%.[18,36] The brain's natural reward mechanisms are regulated by dopamine in the mesolimbic pathway. Consequently, dopaminergic medications – while effective in managing motor symptoms – often can result in secondary behavioural disorders: pathological gambling, binge eating, compulsive shopping and hypersexuality. Other behaviours include repetitive hoarding, substance abuse, punding (repetitive, purposeless behaviours, such as arranging or disassembling objects), kleptomania and impulsive smoking, some of which may be dose-dependent.[36] Impulse control disorders have deleterious consequences on familial, occupation and social functioning.[24] Marital conflicts, loss of vocation and financial difficulties may be direct outcomes; therefore, proper recognition and management of these behaviours are important for the quality of life for both patients and families.[17] Various risk factors may predispose PD patients towards later developing impulse control disorders. These include: younger age of disease onset, male gender, family history of addictive problems, depression, anxiety, and traits such as impulsivity and novelty seeking behaviours.[24] Therefore, identification of premorbid histories in PD subjects is critically important for determining appropriate management strategies with dopamine agonists being avoided in subjects at risk for subsequently developing impulse control disorders. Even in people without premorbid personalities normally associated with impulse control problems, close monitoring is essential for the potential emergence of such side effects.[17]

Challenges and Conclusions

PD is a complex, multisystem disorder. Non-motor symptoms, including psychiatric, correlate with disease severity and advancing age, and therefore are important for our aging population.[14] Neuropsychiatric disturbances negatively affect quality of life and daily functioning for both patients and caregivers and may lead to poor outcomes. In fact, at more advanced stages of PD, non-levodopa-responsive and psychiatric symptoms have been reported as the most disabling aspects of the disease.[37] Including a comprehensive neuropsychiatric assessment may be an important aspect of PD management. However, psychiatric disturbances are under-recognized, and the multiple mental health aspects in PD are difficult to address.[17,24]

Several reasons explain why psychiatric symptoms in PD are often under-reported and under-treated. First, there may be a lack of spontaneous complaints by patients due to unawareness that these are common issues to discuss with their physician.[24] In addition, the obvious social stigma attached to behavioural problems, such as pathological gambling and hypersexuality, may cause patients to hide relevant details from their physician.[17] As a result, psychiatric symptoms may not be promptly diagnosed or overlooked. A survey of 101 patients concluded that depression, anxiety, fatigue and sleep disturbances in PD were under-recognized by the treating neurologists.[38] The diagnostic accuracy for each symptom, as confirmed by standardized testing, ranged from 25-60%. A study in another group of 90 patients demonstrated that depression in PD was only treated in half the cases.[39] Given the time constraint in a doctor's office and low frequency of visits due to wait times, other tools may greatly assist with identification of psychiatric symptoms. For example, patient and self-administered behavioural scales may be routinely included in a unified clinical approach by physicians.[38,39] Ultimately, improving the identification of these symptoms will assist in management of the disease and improving quality of life.

In order to improve recognition of psychiatric disturbances in PD, we need: 1) to educate, patients, families, caregivers and primary care physicians about identifying psychiatric symptoms in PD; 2) a more unified, systematic clinical questioning approach with standardized rating scales to be used by physicians; 3) to fully utilize a collaborative, multidisciplinary healthcare team, including patients and families, with greater psychosocial support for dealing with co-morbidities; 4) to focus greater attention on non-motor symptoms in research studies; and 5) to focus on research that investigates non-pharmacological treatment since polypharmacy and dopaminergic medication may complicate management of psychiatric symptoms.

Is PD just a movement disorder? In addition to motor deficits, psychiatric and a host of other dysfunctions (i.e., autonomic, gastrointestinal, sensory) contribute to the disease.[13] Therefore, it seems the current clinical definition, which is

centralized around motor impairments, is rather limiting. Although our understanding of psychiatric disturbances in PD is incomplete, it is rapidly evolving – as will soon our definition of the disease.

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