

Non-Motor Symptoms and Parkinsonism

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Since the original description in 1817 by James Parkinson, the disease that bears his name has been recognized to be a disorder of the dopaminergic system affecting the substantia nigra pars compacta. Diagnosis of Parkinson disease (PD) has been based on the classical motor symptoms of bradykinesia, rigidity, and rest tremor, and treatment concentrated on dopamine replacement strategies. Using the currently available therapies, most patients experience many years of good motor function, as well as decreased mortality.¹

With the prolongation of life expectancy, it has been increasingly recognized that with disease progression, patients develop a variety of other symptoms that are not responsive to dopaminergic therapy. These include motor symptoms, such as freezing of gait and impairment of balance. Others, termed “non-motor”, include autonomic problems, sleep disorders and psychiatric and cognitive symptoms.² These are due to degeneration of the extradopaminergic systems, not only in the central nervous system, but in the enteric and peripheral nervous systems. Serotonergic, cholinergic, and noradrenergic systems are involved, along with widespread Lewy body deposition.

Most common autonomic symptoms include postural hypotension, bladder urgency and frequency with nocturia, gastric bloating, constipation, bladder and bowel incontinence, sexual dysfunction and dysphagia. Psychiatric symptoms such as depression and anxiety have been reported in over 50% of patients.³ Visual hallucinations, initially benign, are the harbinger of the development of cognitive dysfunction. Up to 70% of individuals will eventually develop dementia. Other common non-motor problems include restless leg syndrome, rapid eye movement (REM) sleep behaviour disorder, fatigue and apathy. All have a significant negative impact on quality of life, which can be greater than motor symptoms, but in the past have been poorly recognized.⁴ For example, postural hypotension can result in falls, and loss of consciousness. Constipation can become so severe that impaction occurs. Hallucinations can become very disturbing and threatening. Early recognition and symptomatic treatment can significantly improve patient outcomes and prevent hospitalization.

With the recognition of the importance of comprehensive assessment of non-motor symptoms, a Non-motor Symptoms Questionnaire was developed.³ This is a 30-item validated questionnaire that can be done by the patient in the office waiting room, and addresses all significant non-motor symptoms.

Non-motor symptoms occur with increasing frequency and severity with disease progression. Their presence early in the disease is useful in ruling out idiopathic PD. For example, the development of significant autonomic symptoms at onset of Parkinsonism suggests multiple system atrophy, early gait and balance problems suggests progressive supranuclear palsy and early cognitive features Lewy body disease. Contrary to this classical teaching, Braak's seminal paper in 2003,⁵ showed that non-motor symptoms can in fact predate the development of motor symptoms of PD. For example, impaired olfaction, REM sleep behavior disorder, excessive daytime somnolence,

constipation, impaired executive function, anxiety, and depression can all occur 5 to 20 years before classical motor symptoms. As these symptoms are non-specific, they cannot currently be used for diagnosis. However, they are garnering increasing interest in order to identify individuals at risk for developing PD, as neuroprotective strategies and disease modifying treatments are being developed.⁶

It is not uncommon to be referred a patient on a dopamine-blocking agent who has developed parkinsonism, the question being whether she/he has drug-induced Parkinsonism or idiopathic PD. This occurs particularly frequently in older individuals as they are more prone to develop parkinsonism on dopamine-blocking agents such as neuroleptics and metoclopramide.⁷ As PD typically affects individuals over the age of 50 and diagnosis is clinical, distinguishing the two conditions is difficult, and involves withdrawing the individual from the offending medication and monitoring the motor symptoms. It should be noted that it may take up to six months for Parkinsonism to resolve in drug induced cases.

In the paper published in this issue of CJNS, Kim et al⁸ asked the question whether assessing the frequency and type of non-motor symptoms can be helpful in distinguishing the two conditions. They enrolled 28 patients with drug-induced Parkinsonism, 35 drug-naïve PD patients in early stages, and 32 healthy controls. Parkinson disease was diagnosed according to classical clinical criteria; some patients additionally had PET scanning to improve diagnostic accuracy. Using the Non-motor Symptoms Questionnaire,³ they were able to determine that a significantly higher proportion of patients in the PD group had non-motor symptoms as compared to the drug-induced group. Looking at the different domains, these included cardiovascular symptoms, sleep disturbances, fatigue, urinary and sexual dysfunction, concentration difficulties, and loss of smell/taste. Of note, the presence of psychiatric symptoms did not differentiate the two groups, as would be expected in a psychiatric population. Thus, the presence of certain non-motor symptoms can be used to help predict diagnosis and prognosis in this patient population.

This is the first study to compare non-motor symptoms in patients with PD in early stages and drug-induced parkinsonism. Their findings suggest that the presence of loss of smell, REM sleep behaviour disorder, fatigue and urinary urgency, may be useful in helping to distinguish PD from drug-induced parkinsonism. Although neuroleptics were studied in this population, this finding would be expected to extend to other dopamine blocking agents, such a metoclopramide. This study further highlights the importance of carefully assessing non-motor symptoms, whether to rule out other neurodegenerative disorders, help confirm a diagnosis of PD, or assess known PD patients for symptoms that require symptomatic treatment to improve function and quality of life.

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REFERENCES

1. Rajput AH. Levodopa prolongs life expectancy and is non-toxic to substantia nigra. *Parkinsonism Relat Disord.* 2001;8:95-100.
2. Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson disease: diagnosis and management. *Lancet Neurol.* 2006;5:235-45.
3. Martinez-Martin P, Schapira AH, Stocchi R, et al. Prevalence of nonmotor symptoms in Parkinson disease in an international setting; study using nonmotor symptoms questionnaire in 545 patients. *Mov Disord.* 2007;22:1623-9.
4. Shulman LM, Taback RL, Rabinstein AA, et al. Non-recognition of depression and other non-motor symptoms in Parkinson disease. *Parkinson Relat Disord.* 2002;8:193-7.
5. Braak H, Del Tredici K, Rüb U, et al. Staging of brain pathology related to sporadic Parkinson disease. *Neurobiol Aging.* 2003; 24:197-211.
6. Lang AE. A critical appraisal of the premotor symptoms of Parkinson disease: potential usefulness in early diagnosis and design of neuroprotective trials. *Mov Disord.* 2011;26:775-83.
7. Thanvi B, Threadwell S. Drug induced parkinsonism: a common cause of parkinsonism in older people. *Postgrad Med.* 2006;85: 322-6.
8. Kim JS, Youn J, Shin H, et al. Nonmotor symptoms in drug-induced parkinsonism and drug-naïve Parkinson disease. *Can J Neurol Sci.* 2013;40(1)36-41.