Non-motor Symptoms in Parkinson's Disease

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease and is responsible for significant morbidity and costs. Non-motor manifestations of PD can be as disabling as the classic motor symptoms. Moreover, medications used to treat PD motor symptoms may have variable effects on these non-motor domains.

Keywords

Parkinson's disease, autonomic function, cognition, dementia, urinary function, sexual dysfunction

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Non-motor symptoms (NMS) in Parkinson's disease (PD) have gained relevance in recent years due to their impact on patient quality of life and their contribution to institutionalisation at an advanced disease stage.[1,2] NMS are present at disease onset and some, such as psychiatric and sleep disorders, may even precede motor symptoms.[3,4] The pathophysiology of NMS is still poorly understood – dysfunction of both dopaminergic and non-dopaminergic systems contribute to their development.

NMS include cognitive and psychiatric dysfunction, disorders of mood and affect, sensory dysfunction, sleep disturbances and various symptoms of autonomic dysfunction (see *Table 1*). Dopaminergic therapy can induce non-motor side effects such as orthostatic hypotension, hallucinations, somnolence and insomnia.[5] Braak and colleagues[6] suggested that degeneration in nuclei involving non-motor domains, primarily the lower brainstem and olfactory systems, may occur before pathology begins in the dopamine nigro-striatal system. This hypothesis has inspired studies to determine whether olfactory changes and changes in sleep patterns may serve, in the future, as pre-clinical markers for PD. While the Braak hypothesis is intriguing in terms of our understanding of the pathological course of PD, NMS remain a major factor in determining quality of life, progression of disability and nursing home placement.

Cognitive Impairment and Dementia

Cognitive dysfunction is quite common in PD patients, while only 30–50% develop a clinically relevant dementia during the disease course.[7] This is different from dementia with Lewy bodies (DLB), where the onset of dementia coincides with Parkinsonian motor symptoms. Cognitive dysfunction in PD is a subtle, slowly progressing process, although some cognitive impairment is often noted much earlier in the course of PD. Additional clinical features observed in cognitively impaired PD patients include hallucinations, psychiatric disorders, daily somnolence and autonomic dysfunction (primarily postural hypotension).

The prevalence of cognitive impairment over the course of PD is difficult to quantify, with reported rates ranging from 8 to 93% depending on the population screened and the tests used.[8] Reported rates of dementia also vary greatly, but it appears that PD dementia (PDD) develops in approximately 30–40% of PD patients. This means that people with PD have a five- to six-fold increased risk of dementia compared with healthy adults.[9,10] The risk of PDD increases with age and disease duration: PDD was diagnosed in 80–90% of patients by the 90 years of age in one study, and in a cohort of patients living with the disease for 20 years 83% were diagnosed with dementia.[11]

Cognitive dysfunction in PD primarily involves impaired working memory and poor performance on visuo-spatial and executive tests; however, memory and language problems may also be observed.

Psychiatric Features – Psychosis and Depression

Psychiatric features are common in PD at all disease stages and depression may even precede motor disability. Depression affects approximately 40% of patients, with some reports as high as 70%, although only 4–6% of patients fulfil the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV) criteria for major depression.[12,13] There is no clear relationship between the degree of motor symptoms (disease severity), age at onset, family history of mood disorders or even past history of depression, and there does not appear to be a correlation with the development of depression in PD. Suicide is unusual, although it has been reported in patients who have undergone deep brain stimulation (DBS) surgery.

Psychosis in PD affects roughly 40% of patients who are receiving dopaminergic therapy and may affect up to 10% of patients who are

Table 1: Non-motor Symptoms at Different Disease Severities in 1,072 Patients Screened in Italy

Non-motor Symptom	Disease Severity as Hoehn and Yahr Score			
	1	1.5–2	2.5–3	4–5
Pain	50.9	58.6	67.1	79.6
Urinary	43.1	51.7	68.3	89.9
Sleep dysfunction	47.9	60.6	75.4	81.6
Fatigue	37.7	56.5	68.9	81.6
Apathy	24.6	26.8	36.6	49.0
Loss of attention	37.7	40.4	51.7	65.3
Skin	14.4	19.8	34.5	32.7
Psychiatric	61.1	63.3	73.2	83.7
Respiratory	9.6	15.5	22.8	30.6
Gastrointestinal	45.5	54.4	76.9	73.5

Sources: Antonini et al., Neurol Sci*, 2008;29(2):61–5 and Barone et al.,* Mov Disord*, 2009;24(11):1641–9.*

not receiving dopaminergic medications. The activity of dopamine in the meso-limbic pathways, along with overall dysfunction in the dopaminergic and serotonergic systems, has been implicated in various types of psychosis and most likely contributes to the psychosis seen in PD patients. Psychosis in PD is primarily characterised by hallucinations (primarily visual hallucinations), delusions and other sensory disturbances such as illusions. PD psychotic events can range from occasional subtle non-disturbing hallucinations, mild illusions and vivid dreams to a psychotic state with disturbing hallucinations and paranoid delusions.[14] When PD patients experience visual hallucinations, they most often consist of people or animals and rarely of inanimate objects.

Sleep Disturbances

Sleep disturbances are frequent non-motor manifestations of PD and involve a complex aetiology, which is often multifactorial in nature. Potential contributing factors can include underlying neurodegenerative processes, loss of sleep due to motor and non-motor features of the disease and sleep-altering effects of drug therapies.

Evidence suggests that the neurodegenerative changes that occur in PD can lead to sleep disturbances very early in the disease process. Such changes may affect sleep structure, leading to sleep fragmentation and the loss of duration of rapid-eye movement (REM) sleep. In fact, longitudinal data to date indicate that REM sleep behaviour disorder (RBD) can precede the motor symptoms of PD, and that RBD may herald the onset of motor symptoms in up to 40% of patients.[15] Interestingly, the severity of sleep disturbance is positively correlated with disease severity, Unified Parkinson's Disease Rating Scale (UPDRS) motor scores, levodopa dose, severity of rigidity and severity of bradykinesia. These correlations underline the complex interplay between sleep disturbance and other manifestations and symptoms of PD.

Excessive daytime sleepiness (EDS) can be observed in approximately 50% of PD patients.[16] Daytime sleepiness is strongly correlated with the use of dopaminergic therapies, which are widely used to treat the motor symptoms of PD. Levodopa and other dopamine agonist therapies have been associated with both EDS and the sudden onset of sleep, and there appears to be a positive correlation with the dose of dopaminergic agents and the occurrence of EDS and sudden onset of sleep.[17]

RBD is characterised by the loss of REM sleep in combination with nocturnal jerking and/or violent limb and body movements. It is speculated that RBD occurs following degeneration of the lower brainstem nuclei, which is characteristic of Braak Stages 1 and 2 of PD progression and may represent a pre-clinical marker of PD.[6] RBD is diagnosed by the presence of limb or body movements while dreaming in addition to at least one of the following: potentially harmful sleep behaviours, dreams that appear to be 'acted out' and sleep disorders that disrupt the sleep continuum. Bed partners often report odd vocalisations and abnormal body movements exhibited by people with RBD. However, morbidity associated with RBD can stretch beyond the sleep disturbance associated with PD, including ecchymosis, lacerations, fractures and even dislocations. In those who experience violent limb and body movements, the risk of injury to bed partners should also be considered.

Autonomic Dysfunction

Autonomic dysfunction in PD consists of a variety of adverse NMS that present due to changes in the activity of the autonomic nervous system. Nearly all people with PD experience one or more of the symptoms associated with autonomic dysfunction. Failure in autonomic function is caused by both the failure of the parasympathetic nervous system – leading to symptoms such as constipation, dry mouth, urinary retention and erectile dysfunction – and sympathetic nervous system failure – with symptoms such as orthostatic hypotension (OH) and thermoregulatory dysfunction.

OH is a particularly disabling NMS of PD that is thought to occur in 20–50% of patients.[18] While people with PD can experience OH at any stage of the disease, it is more common in those with advanced disease. Studies indicate that OH occurs in people with PD due to peripheral sympathetic cardiovascular denervation, which leads to impaired sympathetic input to the cardiovascular system.[19] Symptoms are generalised weakness, dizziness, clouded mentation and even syncope.

Constipation is very common in PD. Studies show that constipation is reported as a prominent complaint before the onset of motor symptoms in approximately 50% of patients. In light of these findings, a prospective study in 7,000 men followed up for a period of 24 years found that those patients with an initial finding of constipation (defined as less than one bowel movement per day) were at a three-fold increased risk of developing PD 10 years after the initial report of constipation symptoms.[20] However, it should be stressed that all PD medications, including levodopa, have been implicated in further slowing of gastrointestinal motility and the exacerbation of gastrointestinal dysfunction, making effective management challenging.

Urinary and/or bladder dysfunction affects over 50% of PD patients with symptoms including increased urinary frequency, urgency and urge incontinence; another 17–27% of patients report urinary hesitancy and/or a weak urinary stream. Urinary symptoms in patients with PD appear to correlate with both severity and duration of disease.[21] Among PD medications, anticholinergics can significantly worsen urinary symptoms.

Erectile dysfunction is a common symptom experienced by male PD patients.[22] Additional sexual symptoms secondary to dopaminergic treatment may also occur in PD patients. Increased libido, hyper-sexuality and aberrant sexual behaviour have been reported in patients receiving dopamine agonist therapies.

Thermoregulatory dysfunction associated with excessive sweating can be very bothersome in PD. Symptoms can include heat and cold intolerance, head and neck sweating and dry skin (particularly on the lower extremities). These symptoms, while less severe than some other symptoms from a medical perspective, have been associated with physical, social and emotional impairment.

Scales to Assess Non-motor Symptoms

Scales have been proposed for NMS evaluation addressing individual aspects such as sleep, cognition, mood, behaviour and quality of life. Recently, the first comprehensive, self-completed NMS questionnaire for PD (NMSQuest) has been developed and validated. It considers 30 items distributed in nine different domains: gastrointestinal, urinary, memory, hallucinations, depression/anxiety, sexual function, cardiovascular, sleep disorders and miscellany. The total number of examined patients is small and additional data are needed to assess the relevance of NMS features for PD disability. Indeed, in the new UPDRS scale, revised by the Movement Disorders Society, non-motor domains have been expanded, reflecting the increasing number of requests from neurologists to better address patient needs. ■

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Related Article

Cognitive Impairment in 873 Patients with Idiopathic Parkinson's Disease. Results from the German Study on Epidemiology of Parkinson's Disease with Dementia (GEPAD)

Riedel O, et al., *J Neurol*, 2008;255(2):255–64.

Parkinson's disease (PD) is often accompanied by non-motor complications such as dementia, depression and psychotic symptoms, which worsen the prognosis and increase the personal and socioeconomic burden of disease. Prevalence estimates of these complications are quite variable and are lacking for the outpatient care sector.

As part of a larger, nationwide, cross-sectional epidemiological study in 315 neurological outpatient settings in Germany, this article estimates the frequency of dementia and cognitive impairment in 873 outpatients meeting the UK Brain Bank criteria for idiopathic PD. Assessments were based on a clinical interview and neuropsychological assessments, including the Hoehn & Yahr rating and Unified Parkinson's Disease Rating Scale (UPDRS). Cognitive impairment was assessed by the Mini-Mental State Exam (MMSE), Clock Drawing Test (CDT) and the Parkinson Neuropsychometric Dementia Assessment (PANDA), and the clinician's diagnosis of dementia was based on the diagnostic criteria of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV).

Using standardised cut-off scores, the prevalence of cognitive impairment in the study sample as measured by various methods was 17.5% by MMSE (≤24), 41.8% by CDT (≥3) and 43.6% by PANDA (≤14), and 28.6% met the DSM-IV criteria for dementia. All estimates increased with age and PD severity. Gender was an inconsistent contributor, while illness duration had no significant impact on cognition. Multiple regression analyses revealed PD severity to be the strongest predictor of dementia risk (odds ratio [OR] 4.3; 95% confidence interval [CI] 2.1–9.1), while neuropsychiatric syndromes had independent although modest additional contributions (OR 2.5, 95% CI 1.6–3.8). Estimates of cognitive impairment and dementia in PD patients are largely dependent on the diagnostic measure used. Using established clinical diagnostic standards for dementia, the overall rate on routine outpatient neurological care is 28.6%, but using more sensitive neuropsychological measures, rates for cognitive impairment might be up to two-fold higher. The MMSE revealed strikingly low sensitivity. Neuropsychiatric syndromes, in addition to PD severity and age, have an independent – although modest – additional contribution to patients' risk of cognitive impairment and dementia. ■