REVIEW ARTICLE

Non-Motor Symptoms of Parkinson's Disease: Diagnosis and Management

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Abstract

***Background**: Non-motor symptoms (NMS) of Parkinson's disease (PD) are a key determinant of health, quality of life (QoL) and societal cost of PD. They are often less appreciated than motor symptoms but are important sources of disability for many PD patients.*

***Methods**: Literature search was performed using the reference databases Medline, Science Citation Index and EMBASE. The keywords used were 'non-motor symptoms', Parkinson's disease, olfaction and constipation. Papers discovered by this search were reviewed, as were references cited therein.*

***Results**: Contrary to common perception, many NMS of PD occur early in PD and some may even predate the diagnosis of PD that is based on motor signs. These include olfactory deficit, sleep problems such as rapid eye movement behaviour disorder, constipation and the more recently described male erectile dysfunction.*

***Conclusion**: There is compelling evidence that non-motor symptoms of PD play a dominant role in the QoL and disability of PD patients and the QoL of their 'informal' carers. Effective clinical management of PD therefore demands that these symptoms be identified and to the extent possible treated.*

***Keywords**: Non motor symptoms, Parkinson's disease, Non motor questionnaire, Constipation, Olfaction, male erectile dysfunction*

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease.[1] Characterized by the cardinal signs of bradykinesia, rigidity, tremor at rest, and abnormalities of balance, posture, and gait, the aetiology of PD remains unknown in most patients.[2] Sir James Parkinson himself recognised Non-motor symptoms (NMS) in PD. Thus, in his essay on the Shaking Palsy in 1817, he referred to sleep disturbance, constipation, urinary incontinence and delirium.[3] NMS in PD, a recognised intrinsic feature of PD, may affect three domains: autonomic, neuropsychaitric, and sensory, including pain.[2] However, despite their impact, the NMS of PD are not well recognised in clinical practise and one study in the United States of America reported that existing depression, anxiety and fatigue are not identified by neurologists in over 50% of consultations, and sleep disturbance in over 40%.[4] Another recent study attempted to correlate NMS in PD at presentation retrospectively after clinico-pathological confirmation of diagnosis.[5] Twenty-one percentage had NMS at presentation and these included pain, anxiety, urinary dysfunction and depression. It is commonly thought that NMS occur only in late or advanced PD but NMS can indeed present at any stage of the disease including early and pre-motor phase of PD. Prospective data based on the Honolulu Asia ageing and other studies suggest that several NMS of PD such as olfactory problems, constipation, depression and erectile dysfunction may predate the motor signs, symptoms and diagnosis of PD by a number of years.[6,7] These data indicate that NMS may appear early in the course of PD and dominate the later stages of the disease. It has been suggested that some NMS such as olfactory dysfunction in combination with others such as rapid eye behaviour disorder (RBD) or constipation may form part of a battery of tests to identify a population "at risk of PD", which will be particularly important if and when neuroprotective therapies become available (Table 1). Stacy and co workers[8] reported that NMS were present even in patients within 5 years of motor disease onset, and these were identified frequently with the use of a patient-completed questionnaire. A comprehensive, self-completed non-motor questionnaire for PD (NMSQuest) was developed to help identify NMS.[9] A range of non-motor symptoms occurred in PD patients from early to advanced disease. The NMSQuest flagged up many NMS such as dribbling of saliva, dysphagia and sexual problems that had not been discussed with a doctor earlier. The study also highlighted that, irrespective of country of study and disease stage, most PD patients are likely to flag up 9 to 12 different NMS in the NMSQuest at clinic visit.[10] Further studies validating the first dedicated scale for

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NMS of PD, the PD non-motor scale (NMSS), have indicated a strong relationship between the burden of NMS in PD and health-related QoL. [10] The exact pathophysiology of NMS is still poorly understood. Recent pathological evidence suggests that PD affects the brain in six stages. [11] The first two preclinical are characterized by abnormalities in the olfactory bulb and lower brain stem. Several NMS, including loss of smell, sleep disturbances, and fatigue may occur during these first stages and are preclinical markers of the disease. Tremor, rigidity, and bradykinesia become evident in stages 3 and 4 when the substantia nigra pars compacta is affected. The neocortex and limbic system are affected in stages 5 and 6, which may cause dementia and hallucinations. Screening these early NMS might, therefore, be one approach towards early 'preclinical' diagnosis of PD. This review article provides an overview of the clinical spectrum of NMS in PD together with a brief review of treatment options.

Table I A list of non-motor symptoms suggested as pre-clinical (motor) features in Parkinson's disease

Constipation
Olfactory deficit: (discrimination)
REM behaviour disorder
Depression
Possible links
Restless legs syndrome
Apathy
Fatigue
Anxiety
Pain
Male erectile dysfunction

Sleep Disorders

Sleep disorders affect nearly all PD patients, appear early in the clinical course of PD. They include insomnia, parasomnias, RBD, restless legs syndrome, periodic limb movements of sleep, vivid dreaming, and sleep apnea. In addition, patients may experience disorders of wakefulness, including excessive daytime sleepiness or sudden-onset sleep (sleep attacks) with or without concomitant sleep disorders.

Excessive daytime sleepiness (EDS) commonly occurs in PD and frequently adversely affects QoL. EDS can be caused by the disease itself, medications, or sleep disorders. Predictors of EDS in PD include increasing age, advanced disease and higher dosages of doperminergic medications. Dopamine agonists (DAs) in particular are a common cause of EDS in patients with PD.[12, 13] A careful medication review and sleep history are warranted for patients with EDS. Assessments that can be useful include Parkinson's Disease Sleep Scale [14], SCOPA sleep [15], and Epworth Sleepiness Scale (not specific for PD). [16] If no treatable sleep disorder is identified, treatment with modafinil or other wake-promoting agents can be considered. [13, 17, 18] Several trials have evaluated the use of modafinil, a wake-promoting agent that is approved for use in narcolepsy, for treating EDS in PD. Results of these trials are conflicting and range from modest improvement to lack of efficacy. The dose range of modafinil in these studies was 200 mg/day to 400 mg/day.

Insomnia is very common in PD and causes patients to be unable to fall asleep or maintain sleep. It can be treated by having the patient adhere to a consistent sleep schedule, attempt to avoid daytime napping, and abstain from alcohol, caffeine, tobacco and other stimulants in the evening hours. [19] A review of all current medications is warranted to identify those that might be causing insomnia. Depression and anxiety should be treated. Some patients may require the use of hypnotics such as zalepion or trazadone to treat insomnia.

REM sleep behaviour disorder (RBD)
RBD is a parasomnia characterized by loss of normal skeletal muscle atonia during REM sleep when dreaming occurs, leading to “acting out of dreams,” including sleep talking, shouting, and intense, sometimes violent movements. Patients may inadvertently injure their bed partners by punching or choking them. [20] RBD has been reported in 25% to 50% of patients with PD and can precede the onset of PD by several years.[21, 22] Clonazepam can be used in dosages of 0.5 mg to 2 mg at bedtime to treat RBD.

Restless legs syndrome

The syndrome of restless legs occur in approximately 20% of patients with PD. [23] It causes patients to experience an urge to move their legs, usually accompanied by uncomfortable leg sensations. It is common in the elderly in Western populations, in which restless legs syndrome affects 8 to 10% of subjects over 65 years of age. [24, 25] DAs, including ropinirole and pramipexole may be used to treat restless legs syndrome in PD. Opiods can also be used but may cause dependency.

Fatigue

Fatigue has been reported in 75% PD patients [26] and is more prevalent in patients with PD than in age-matched controls. It is characterized by a feeling of lack of energy with consequent degradation in functional ability and

QoL. The cause of fatigue in PD is unclear, and it does not clearly correlate with the severity of motor symptoms, depression, or dosage or duration of PD medications.[27] Assessment that can be useful include Fatigue Severity Scale [28] and Parkinson Fatigue Scale (PFS-16)-self report [27] Treatment for fatigue in PD have not been well evaluated, although modafinil and other stimulants have been used anecdotally.

Sleep Apnoea

Obstructive sleep apnoea occurs in about 20% of patients with PD[29] and is defined by intermittently absent or reduced airflow during sleep despite respiratory effort. However, patients may not give a history of snoring, and there is a suggestion that PD patients with sleep apnoea need not be obese. Treatment usually consists of wearing an airflow mask, although many patients find it uncomfortable.

Autonomic dysfunction

The prevalence of orthostatic dizziness, constipation, bladder dysfunction, erectile dysfunction, and hyperhidrosis is significantly higher among PD patients than matched controls.[9] Orthostatic hypotension is defined as a drop of 30 mmHg in systolic blood pressure or a drop of 20 mmHg in mean blood pressure when rises to standing from supine position. Orthostatic hypotension and dizziness are associated with an increased risk of falls and resulting fractures. Treatment consists of adequate hydration with eight or more glasses of fluid each day, and the use of mineralocorticoids, such as fludrocortisone, to increase intravascular volume. [30] Other frequently experienced autonomic symptoms in a prospective clinic-based survey of patients with six years of disease duration and more advanced disease were hypersalivation (14%), sexual dysfunction (18%), urinary problems (22%), sweating disorder (24%) and constipation (59%). [31] Potentially useful assessment of autonomic dysfunction include: SCOPA-AUT- a questionnaire to evaluate autonomic dysfunction in Pd[32], QSART- quantitative sudomotor axon reflex for sudomotor function and urodynamic studies for uroflowmetry and cystometry.

Cognitive impairment and dementia

Cognitive impairment may be present even in the early stages of PD. Estimates of the prevalence of cognitive impairment in PD range from 20% to 93% depending probably on how cognitive impairment is defined and assessed. In a community-based survey in early PD, 36% of the patients had evidence of cognitive impairment at diagnosis. [33] The cognitive profile in patients with the disease varies somewhat, but executive impairment, including working memory and attention shift, and visuo-spatial dysfunction characterize early cognitive impairment in PD. [34] Dementia in PD is associated with longer disease duration and older age at onset and is a risk factor for nursing home placement and is associated with shorter life expectancy. [35] Assessments that can be useful include SCOPA-Cog-[36] a short, reliable instrument sensitive to the specific cognitive deficits in PD and Mini-Mental State Examination (MMSE). [37] Although commonly used to screen for cognitive decline, the MMSE has not been specifically validated in PD and parts requiring a degree of motor skill should probably be discounted. Rivastigmine, a cholinesterase inhibitor, is now approved for use in treating dementia in PD. In a placebo-controlled study, PD patients with mild to moderate dementia were randomly assigned to receive placebo or 3 mg to 12 mg of rivastigmine per day for 24 weeks. [38] Moderate improvements in dementia were noted with rivastigmine use, but there were also higher rates of nausea, vomiting and tremor. Despite the growing literature suggesting benefits of cholinesterase inhibitors therapy, more studies are needed to clarify whether differences exist among the various cholinesterase inhibitors.

Other neurobehavioral disturbances

Neuropsychiatric disorders are important determinants of QoL and caregiver burden in PD. [39] In a population-based study of 139 patients with PD, 61% suffered from at least one neuropsychiatric symptom after 12 years of disease duration. [40] The most common behaviours found were depression (38%) and hallucinations (27%).

Psychotic symptoms in PD (PDPsy) include illusions, the sense of presence, simple and complex hallucinations with and without insight, and delusions. Visual hallucinations are found to be the most common form, while auditory, olfactory and tactile hallucination are less frequent and usually present together with visual hallucination. [41, 42, 43] PDPsy in patients with PD rarely occurred before the introduction of dopaminergic treatment.[44, 45] Dopaminergic agents are therefore understood as an important cause of psychotic symptoms and abnormal behaviour in PD. Reported prevalence rates of hallucination vary, most likely due to differences in patient selection and study design, and range from 16% to 75% in prospective cross-sectional studies.[45] Hallucinations are one of the main features causing hospitalization and nursing home placement in patients with PD. [46]

Depressive symptoms are significantly more common in PD than in age-matched controls and patients with other chronic diseases.[47, 48] They may occur many years before the motor onset of PD. [49] About 20% of patients report depressive symptoms before diagnosis, and the risk for developing PD is 2-3 fold increased in depressed patients compared to non-depressed control subjects.[47, 50, 51] In a recent systematic review of prevalence studies of depression in PD, frequency rates ranged from 12.7% to about 90% in clinical-based studies fulfilling quality criteria for inclusion. [52] This variation is likely to be the result of methodological differences between studies in the studies included. Antidepressants, including tricyclics and selective serotonin reuptake inhibitors (SSRIs) have been found to improve depression in patients with PD, and the DA pramipexole may have antidepressant efficacy.

Olfactory dysfunction

Olfactory dysfunction in PD includes impairment of odour detection, differentiation, and identification, and is persistent and not influenced by drug treatment. [53] In the light of Braak's hypothesis of a stagewise progression of pathological changes in PD, indicating presymptomatic lesions in the olfactoric tract, attention has been drawn to patients primarily diagnosed with idiopathic hyposmia. Recent evidence suggests that these persons are at increased risk of developing PD later during life.[54, 55] Olfactory dysfunction is increasingly recognised as a frequent feature in overt PD [56], but its prevalence in the general PD population is unknown. Most patients showing deficits in olfactory tests are unaware of a smell disorder.[56]

Impulse control disorders

Several complications apparently related to high-dose dopaminergic treatments for PD are comparatively infrequent, but deserve attention because they are socially disabling when they occur.

Punding involves compulsive, stereotypical, repetitive and purposeless behaviours that are similar, but distinct from obsessive-compulsive disorder. In a series of 50 patients with higher dopamine replacement therapy (>800 levodopa [L-dopa] equivalent units/day), from 123 unselected PD patients Evans et al [57] identified 17(14%) patients with punding. Management of punding involves reduction of dopaminergic doses. In a report of three cases, Meseguer [58] reported improvement in all with reduction of dopaminergic doses. There is neither any specific scale nor screening instrument to assess punding nor common diagnostic criteria. Clinicians will need to rely upon interviews as patients with punding appear to be aware of their behaviour but information from caregivers may be most helpful.

Pathological gambling is one of the impulse control disorders that can have disastrous consequences and is related to dopaminergic agonists. [59] In a series of 297 PD patients and using rigorous criteria for impulse control disorders (ICDs), Voon et al [60] found lifetime prevalence of 3% for pathological gambling, 2.4% for pathological hypersexuality and 0.7% for compulsive shopping, giving lifetime prevalence of these ICDs of 6.1%, which increased to 13.7% in patients on dopamine agonists.

Treatment of non-motor symptoms

There is an association between the severity of motor symptoms and the incidence of non-motor symptoms, but the relationship is weak and non-motor symptoms are characteristically unresponsive to L-dopa. 61 Because NMS are generally unresponsive to dopaminergic drugs, clinical management will require interventions commonly used to treat the emergent symptom, but keeping in mind that PD patients are often elderly, at risk for drug-drug interactions and often require doses differing from those for healthy adults.

Summary and conclusions

PD is the second most common neurodegenerative disorder. Non-motor features such as constipation, olfactory dysfunction, depression, anxiety, and sleep disorders may precede the motor onset of the disease. There is compelling evidence the NMS of PD play a dominant role in the QoL and disability of PD patients and the QoL of their 'informal' carers. Effective clinical management of PD therefore demands that these symptoms be identified and to the extent possible, treated. Treatment can be challenging, as these symptoms are often unresponsive to conventional dopaminergic therapy. However, the importance of a multi-professional team-neurologist, specialist nurse, physio- and occupational therapists-is essential for providing optimal care.

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