REVIEW ARTICLE

http://dx.doi.org/10.14802/jmd.15003 / J Mov Disord 2015;8(2):92-97
pISSN 2005-940X / eISSN 2093-4939

# Many Faces of Parkinson's Disease: Non-Motor Symptoms of Parkinson's Disease

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## ABSTRACT

Parkinson's disease (PD) is a multi-systemic disorder that is characterized by a combination of motor and non-motor symptoms (NMS). The dopaminergic neurodegeneration of PD is involved in the genesis of NMS, but other conditions and side effects of levodopa are also associated with NMS. NMS can develop at all stage of PD and rapid eyeball movement sleep behavior disorder (RBD), constipation, depression, and olfactory dysfunction are considered prodromal signs of PD. Many NMS related with motor deficits and cognitive dysfunction. Some NMS including olfactory dysfunction, RBD and abnormal stereopsis are associated with presence of other NMS of PD. In addition, several NMS can be helpful to differentiate between idiopathic PD and other parkinsonian disorders. Early recognition and management of NMS in PD patients is important for preserving quality of life.

Key Words
Parkinson's disease; Non-motor symptoms.

**Received:** January 28, 2015 **Revised:** January 28, 2015
**Accepted:** February 12, 2015
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## INTRODUCTION

Parkinson's disease (PD) is considered a multi-systemic neurodegenerative disorder that is characterized by a combination of motor and non-motor symptoms (NMS).[1,2] For a long time the main clinical focus in PD has been on the motor symptoms, however, there is increasing recognition that the clinical spectrum of PD is more extensive, also including NMS. NMS of PD comprised a variety of cognitive, neuropsychiatric, sleep, autonomic, and sensory dysfunctions.[3] Neuroanatomically, NMS may be subdivided into cortical manifestations (psychosis and cognitive impairment), basal ganglia symptoms (impulse control disorders, apathy, and restlessness or akathisia), brainstem symptoms (depression, anxiety, and sleep disorders), and the peripheral nervous system disturbances [orthostatic hypotension (OH), constipation, pain, and sensory disturbances].[4] Another way of classifying NMS is to divide it by the contributing factors.[5,6] Some NMS correlated with accumulation of Lewy body pathology and disease severity[3,5] and other NMS are known as dopamine replacement therapy related symptoms.[7,8] Additionally, some NMS including rapid eyeball movement sleep behavior disorder (RBD), constipation, depression and olfactory dysfunction can be present in prodromal PD.[9] Recently NMS are recognized as an important part of PD symptoms which is a significant cause of disability and poor quality of life for PD patients and receiving medical attention as a focus of care.[10-12] This manuscript will review the literature on NMS and provide some educational issues about NMS of PD and other parkinsonian disorders.

## SCALES FOR NMS ASSESSMENT

The assessment of NMS in patients with PD is essential for proper management. There are specific validated tools available for their assessment. The Unified Parkinson's Disease Rating Scale is an easy-to-use instrument and extensively applied to clinical trials of early PD.[13] It includes a few items for NMS but has a limited application because it reliably completed by non-demented patients. The Scale for Outcomes in Parkinson's disease (SCOPA) battery of assessments consists of seven sub-rating scales that cover almost all symptom domains of PD (PROfiling PARKinson's disease or PROPARK) (http://www.scopa.propark.eu). It was designed to be short, practical to administer, and either self-assessed or observer-administered. The non-motor symptoms questionnaire (NMSQ) is a self-administered screening tool comprising 30 items of NMS.[14] It is used to identify presence of NMS for further investigation and does not provide a severity of symptoms and an overall score. The non-motor symptoms scale (NMSS) is observer-rated scale consists of 9 domains, 30 items.[15] It was designed to quantify clinically significant NMS by measuring the frequency and severity of NMS. The NMSS translated into Korean exhibited good validity for the assessment of NMS in Korean PD patients.[16]

## NMS AS PREMOTOR SYMPTOMS

Many studies suggest there is a prodromal or premotor stage of PD before the onset of motor symptoms. Because the early occurrence of NMS correlates with the progression of Lewy body pathology[17] and even dopaminergic cell loss in subtantia nigra occurs from the premotor stage,[18] identifying early PD as a target of neuroprotective treatment is spotted. Some NMS including olfactory dysfunction, RBD, constipation, and depression may precede the development of motor symptoms of PD and are considered prodromal signs before diagnosis of classical PD.[9,19] In addition, visual changes, autonomic dysfunction, and subtle cognitive changes may also be present at prodromal stages of PD.[9]

## RELATIONSHIP BETWEEN NMS AND DOPAMINE REPLACEMENT THERAPY

The motor symptoms can be classified with the levodopa responsiveness. Bradykinesia and rigidity are most likely to get better with levodopa, while axial problems such as balance, speech and gait disturbance do not show adequate response to levodopa compared to bradykinesia and rigidity. In the same manner, NMS can be classified with the relationship of dopaminergic treatment (Table 1).[20,21] Recent positron emission tomography study suggests a dopaminergic contribution to some NMS[22] and such symptoms related to the dopamine replacement therapy (DRT). Because levodopa may modify striatal serotonin level,[23] some non-dopaminergic NMS also

**Table 1.** Non-motor symptoms of Parkinson's disease and their responsiveness to dopamine therapy[26]

| | Responsive to DRT | Unresponsive to DRT | Induced by DRT |
|---|---|---|---|
| Neuropsychiatric symptoms | Depression<br>Apathy<br>Anxiety<br>Anhedonia<br>Off period related panic attacks | Cognitive dysfunction<br>Attension deficit<br>Dementia<br>Confusion | Hallucination<br>Delusion<br>DDS<br>Punding<br>ICD |
| Sleep disorders | RLS<br>PLM<br>RBD* | Non-REM sleep related movement disorders<br>Vivid dreaming<br>Insomnia<br>Sleep-disordered breathing | EDS |
| Autonomic symptoms | Urgency (detrusor overactivity)<br>Nocturia<br>Erectile dysfunction | Frequency<br>Sweating | Orthostatic hypotension |
| Gastrointestinal symptoms | Dribbling of saliva*<br>Constipation<br>Unsatisfactory voiding of bowel | Ageusia<br>Dysphagia<br>Reflux, vomiting<br>Fecal incontinence | Nausea<br>Diarrhea |
| Sensory symptoms | Primary pain (central pain)<br>Fluctuation-related pain | Secondary pain<br>Paresthesia<br>Olfactory disturbance<br>Visual dysfunction | |
| Other symptoms | Non-motor fluctuations<br>Fatigue | | Ankle swelling<br>Blurred vision |

*some anecdotal reports of response to dopaminergic treatment. Some unmarked symptoms might also respond to treatment. DDS: dopamine dysregulation syndrome, DRT: dopamine replacement therapy, EDS: excessive daytime sleepiness, ICD: impulse control disorders, PLM: periodic limb movement, RBD: rapid eyeball movement behavior disorder, REM: rapid eyeball movement, RLS: restless legs syndrome.

respond to DRT. However, many NMS occur as a result of dysfunction of various neurotransmitters, they require different treatments rather than DRT.

## RELATIONSHIP BETWEEN NMS AND MOTOR SYMPTOMS

The postural instability gait difficulty (PIGD) subtype of PD has been reported to be associated with NMS. Patients with the PIGD subtype were related to faster cognitive decline[24] and more frequent depression.[25] Recent study suggests that patients with higher scores of motor symptom experienced greater numbers of NMS and among them, patients with the PIGD subtype had higher NMSQ scores than patients with other subtypes.[26] Fluctuation of motor symptoms in PD also has relation to NMS. PD patients with motor fluctuation were related with more anxiety.[25] Anxiety, depression, fatigue, inner restlessness, pain, concentration/attention and dizziness were known to fluctuate in conjunction to motor fluctuations with more frequent and severe symptoms in 'off' compared to 'on' state.[27] The patterns of these NMS fluctuations are heterogeneous and complex, but psychic NMS fluctuate more frequently and severely.[27] However, the study revealed no correlation between the severity of NMS and motor function.[27] In addition, there is a close relationship between sensory dysfunction and motor signs. Higher-order discriminative sensory dysfunction seems to contribute in part to the development of axial motor deficits in PD.[28] The discriminative sensory dysfunction and consequent abnormal sensorimotor integration seem to be involved in the impaired finger dexterity (coin rotation test) of PD.[29] A study on dysfunction of special sensory in early PD patients revealed postural instability caused by sensory organization defects (visual & vestibular processing) seem to be related with motor deficits and cognitive dysfunction.[30]

## INTERRELATIONSHIP AMONG NMS

Several studies have reported the interrelationship among some NMS. Olfactory dysfunction in PD was known to be related to both cardiac sympathetic and parasympathetic dysfunction measured by the heart/mediastinum ratio of cardiac 123I-MIBG uptake, the fall in orthostatic blood pressure, and heart rave variability.[31] Olfactory dysfunction was also associat-

ed with postganglionic cardiac and organ-selective extracardiac noradrenergic denervation as indicated by concentration ratios of 6-[18F] fluorodopamine-derived radioactivity in heart versus other organs and by low concentrations of norepinephrine and dihydroxyphenylglycol levels in skeletal muscle microdialysate samples.[32] One study suggested that PD patients with RBD were at higher risk of manifesting hallucinations and delusions.[33] However, the other study reported that the presence of RBD was associated with symptoms, signs and prevalence of OH but not associated with psychotic symptoms.[34] Other independent clinical factors found to have an effect on psychotic disorders were cognitive impairment and autonomic dysfunction.[33,35] Cognitive impairment is also related to neurocirculatory abnormalities, especially OH and supine hypertension in early PD.[36] PD patients with abnormal stereopsis showed more frequent abnormal visual perception and constructive function compared to patients with normal stereopsis.[37] Abnormal stereopsis is associated with non-dominant extrastriate cortical atrophy and that it implicates the cortical visual dysfunction as part of the nonmotor symptoms in PD.[38]

Cognitive impairments are common in PD. Despite its clinical importance, the development of dementia is still difficult to predict. Vivid dreaming, RBD, hyposmia, abnormal stereopsis, and depression were significant NMS PD dementia predictors at 24 months in one study.[39] These NMS are also associated with a more rapid rate of cognitive decline.

## NMS IN OTHER PARKINSONIAN OR MOVEMENT DISORDERS

Non-motor symptoms has been investigated in other neurodegenerative disorders associated with parkinsonism. Olfactory dysfunction corresponds to neuropathological findings of Lewy bodies in the anterior olfactory nucleus.[40] Olfactory dysfunction tested by the University of Pennsylvania smell identification test (UPSIT) was found to be mildly impaired in multiple system atrophy (MSA),[41,42] and normal in progressive supranuclear palsy (PSP),[41] corticobasal degeneration,[41,42] and vascular parkinsonism.[43] The UPSIT was moderately sensitive and specific for differentiation of idiopathic PD from other parkinsonian syndrome but less specific for distinguishing idiopathic PD from MSA.[44] Instead, early presentation of autonomic failure, sleep problems and respiratory dysfunctions/stridor are regarded as premotor signs for diagnosis of MSA.[45] In patients with drug induced parkinsonism (DIP) unrelated to PD, olfactory function assessed by the cross cultural smell identification test and cardiac 123I-metaiodobenzylguanidine uptake were normal.[46] Urinary symptoms, excessive daytime sleepiness, restless legs syndrome, attention deficit, and hyposmia were associated with PD and may be helpful to differentiate between DIP and PD in the early stages.[47] Essential tremor patients had significant cognitive dysfunction, neuropsychiatric problems including depression and have complained about significant autonomic dysfunction and excessive daytime somnolence compared to normal controls. Patients with ET have several NMS similar to those of patients with PD, which have a similar impact on their quality of life.[48]

## NMS AND QUALITY OF LIFE

Non-motor symptoms and levodopa-resistant motor symptoms dominate the clinical picture and disability of patients with late stage PD.[49] The scores of Korean version of 39-item Parkinson's disease questionnaire (PDQ-39), instrument for evaluating health-related quality of life (HrQoL) in PD patients, demonstrated significant relationships with NMSS scores.[50] The NMSS scores also significantly correlated with PDQ-39 scores in patients with MSA and PSP.[51] NMS progression contributes importantly to HrQoL decline[52] with a growing emphasis on the importance of HrQoL when managing PD patients.

## CONCLUSIONS

Non-motor symptoms in PD have close relationship with motor signs and are now recognized as an integral component of multisystem disorder. NMS often carry a greater impact than motor signs in PD, especially in the late stage of PD. Although many NMS are resistant to levodopa treatment, optimizing dopaminergic therapies is viable avenue to improve control of some disabling NMS in PD. In recognition and treatment of NMS are increasingly emphasized in the care of PD patients.

## Conflicts of Interest

The authors have no financial conflicts of interest.

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