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Parkinson's Disease: Focus on Non Motor Symptoms.

Kuljeet Singh Anand, *Rohit Verma

Department of Neurology, PGIMER Dr Ram Manohar Lohia Hospital, New Delhi

*Department of Psychiatry, All India Institute of Medical Sciences, New Delhi

Abstract : Although Parkinson's disease (PD) is the 2nd most common neurodegenerative disorder, the recognition of various non-motor symptoms (NMS) has been frequently overlooked with the motor symptoms of PD taking precedence for diagnostic and treatment approaches. NMS herald the progression of the disease, at times even before the motor symptoms appear, and are pathologically represented by involvement of brain areas other than the classical nigrostriatal region, with differential involvement of degeneration. There is an urgent need to address this pertinent issue to cater the patient's as well as the caregiver's quality of life which can drastically improve with appropriate management of NMS.

Keywords: Parkinson, non motor, NMS, neurodegenerative.

INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder second only to Alzheimer's disease.¹ The cardinal clinical features of PD include asymmetric onset of bradykinesia, rigidity, and resting tremor resulting from the loss of dopaminergic neurons in substantianigra pars compacta (SNc).² The peak age of onset of PD is in the early 60s (range 35-85 years), and the course of illness ranges from 10 to 25 years.³

The prevalence of PD is estimated to be 329 per lakh general population, and an annual incidence ranging from 16-19 per lakh general population with estimates of 5 million sufferers worldwide.⁴ The prevalence increases with age, affecting about 1-2% of adults 60 years and older to greater than 4% of adults above 80 years.⁵ The current incidence is expected to double by year 2030.⁴

Correspondence: Dr. Rohit Verma, Department of Psychiatry, All India Institute of Medical Sciences, New Delhi
email: rohit.aiims@gmail.com

Patients with PD often have non-motor symptoms (NMS) in addition to the motor manifestations. These NMS have recently been recognized and systematically described.⁶

There is increasing realization that NMS significantly contribute to the morbidity and increase the burden of the disease far beyond that caused by the classical motor symptoms.⁵

The current review will focus upon this increasingly recognized entity of NMS in PD.

PATHOPHYSIOLOGY

While the motor symptoms of PD bear a direct correlation to the presence of neuronal degeneration in the SNc, they do not represent the true beginning of the degenerative process, as NMS can occur prior to presence of such abnormalities in SNc.⁷ With emergence of functional and neuropathological studies, there has been recognition of involvement of areas apart from the nigrostriatal region.⁷

Many NMS precede the appearance of classic motor manifestations as a prodrome to the eventual illness. Olfactory dysfunctions,

gastrointestinal disturbances, sleep difficulties, depression and multiple cognitive deficits.⁸⁻¹³

The seminal work by Braak and colleagues suggested that the degenerative process begins in non-dopaminergic structures of the brain stem, even in the peripheral autonomic system.⁹The authors suggested that the degenerative process starts in the caudal regions of the brainstem (dorsal motor nuclei of the glossopharyngeal and vagus nerves) and the olfactory bulb, progressing in the caudal-rostral direction with the involvement of SNc later in the disease. Degeneration of other brain-stem nuclei follow the appearance of motor signs, until finally the degenerative process reaches the anteromedial temporal cortex and then the neo cortex, starting with associative and pre frontal, until finally sensory, motor and pre motor areas are affected.

However, other researchers have not observed the occurrence of this peculiar sequential pathological distribution.^{14,15}The study though caveated with deficiencies paved way for motivation towards dissemination of the concept of the existence of NMS in PD. Pathological heterogeneity has been observed between early and late onset PD manifesting as clinical subtypes among motor and non-motor PD.¹⁶There has been a growing evidence of involvement of a non-dopaminergic process as the key to NMS in PD.^{7,17}Table 1 suggests some of the hypothetical pathological changes leading to NMS in PD.

Table 1: Suggested pathogenesis causing NMS in PD

NMS	Pathogenesis
Olfactory dysfunction ^{9,12}	Non dopaminergic degeneration of the olfactory bulb and other related nuclei
Gastrointestinal disturbances ¹⁸	Pathology in the enteric system
Sleep disturbances ¹⁹	Changes to multiple neurotransmitter systems of the brainstem
Depression ⁸	Involvement of locus coeruleus and raphe nuclei, which provide noradrenergic and serotonergic innervation to the cerebral cortex and limbic system
Autonomic dysfunction including Orthostatic hypotension ²⁰	Degeneration of the sympathetic cardiac and vasomotor systems
Cognitive deficits ¹¹	Changes in dopaminergic and cholinergic systems
Dementia ²¹	Extension of Lewy Body pathology to the cerebral cortex
Central pain ²²	Lesions in thalamus

NMS – CLASSIFICATORY APPROACH

The widespread NMS of PD comprise a variety of cognitive, neuropsychiatric, gastrointestinal, sleep, autonomic, and sensory dysfunctions.²³With emergence of newer understanding of NMS and motor symptoms, approaches are on way to amend the currently utilized brain bank motor diagnostic criteria.²⁴ Table 2 lists some of the proposals to classify NMS in PD.^{17,23,24}

EPIDEMIOLOGY

Despite its importance and frequency, NMS are not adequately recognized in clinical practice. One study reported that depression, anxiety, fatigue, and sleep disturbances are not identified in almost 50% of visits to the treating neurologist.²⁵ Another study reported similar figures of almost 43% of NMS being missed in the neurology consultation.²⁶

As the life expectancy of patients of PD has now increased, cognitive

Table 2: Classificatory approach towards NMS in PD:

Classificatory basis	Typology
Related to the disease process or pathophysiology	Dopaminergic origin Non-dopaminergic origin ⁸
Related to a partial non-motor origin	Usually brainstem autonomic impairment with motor end result, such as constipation or diplopia
Related to non-motor fluctuations (cognitive, autonomic and sensory subtypes)	Fluctuating ⁸ Constant
Related to PD drug therapy	Specific symptoms (eg, hallucinations, delirium) ⁸ Syndromes—impulse control disorders, dopamine agonist withdrawal syndrome, Parkinson's hyperpyrexia syndrome (thermoregulatory failure, delirium)
Possibly genetically determined	Dementia in cases with glucocerebrosidase mutation Depression and sleep disorders in cases with β leucine-rich repeat kinase-2 mutation
Related to neuroanatomical distribution	Cortical manifestations (psychosis and cognitive impairment) Basal ganglia symptoms (impulse control disorders, apathy, and restlessness or akathisia) Brainstem symptoms (depression, anxiety, and sleep disorders) Peripheral nervous system disturbances (orthostatic hypotension, constipation, pain, and sensory disturbances)
Division by the contributing factors	NMS related with accumulation of Lewy body pathology and disease severity NMS related to dopamine replacement therapy related symptoms
Early and late occurrence	Prodromal PD – commonly associated with Rapid eye ball movement sleep behavior disorder (RBD), constipation, depression and olfactory dysfunction Late NMS - complicate the clinical picture throughout the disease (pain, fatigue) and especially in its advanced stages (dementia, apathy, dysautonomia)

dysfunction and dementia associated with the disease are more often observed. In one study it was found that 36% cases in an incident cohort of PD patients had evidence of cognitive impairment.²⁷ Even in absence of dementia, mild cognitive impairment is observed in 19% to 38% of patients with PD.²⁸ Depression is common in PD, occurring in up to one-half of the patients. Anxiety disorders may be as common as depression and the two are frequently co-existent.²⁹ Apathy, may overlap, but is usually distinct from depression. In addition, suicidal ideations, hallucinations, and delusions may occur.³⁰ When PD patients are carefully questioned, it becomes evident that fatigue, sleepiness, and sleep disturbances are major problems independent of any medication and motor disability. Studies have shown that sensory symptoms, such as pain and anosmia, may precede the development of PD, sometimes by many years.³⁰ Autonomic dysfunction occurs prominently and is seen in about nine out of ten patients with PD, which appear to increase significantly with increasing disease severity.³¹ Table 3 describes the various NMS associated with PD.

Table 3: Various NMS described in PD

Neuropsychiatric symptoms	Depression, apathy, anhedonia, anxiety, panic attacks, attention deficits
	Hallucinations, illusion, delusions, Obsessional behavior
	Dementia, confusion, delirium
Sleep disorders	Restless legs and periodic limb movements, REM sleep behavior disorder (RBD) β Insomnia, excessive daytime somnolence β Vivid dreaming, sleep disordered breathing
Autonomic symptoms	Bladder disturbances: urgency, nocturia, frequency
	Sexual dysfunction: hypersexuality, erectile dysfunction Abnormalities of sweating, orthostatic hypotension, dry eyes (xerophthalmia), dry mouth
Gastrointestinal symptoms	Dribbling of saliva (sialorrhea) β Delayed gastric emptying, agusia, dysphagia, choking, reflux β Vomiting / nausea (usually drug related) β Constipation / unsatisfactory voiding of bowel / faecal incontinence
Sensory symptoms	Pain / paraesthesia, olfactory disturbance (hyposmia)
Other symptoms	Fatigue, diplopia, blurred vision, seborrhea, weight loss, weight gain

*Adapted from Chaudhuri et al. (2005)³²

MANAGEMENT OF NMS

There are various approaches to manage NMS in patients with PD. Table 4 provides the commonly prescribed pharmacological and non-pharmacological approaches to manage various NMS associated with PD.

Table 4: Management techniques for NMS

NMS		NON PHARMACOLOGICAL MANAGEMENT	PHARMACOLOGICAL MANAGEMENT
Neuro-psychiatric disorders	Depression	<input type="checkbox"/> Awareness of non-motor fluctuation <input type="checkbox"/> Counseling <input type="checkbox"/> Psychotherapy	<input type="checkbox"/> Pramipexole <input type="checkbox"/> SSRI – Paroxetine, Citalopram <input type="checkbox"/> SNRI – Venlafaxine <input type="checkbox"/> TCA – Nortriptyline, Desipramine <input type="checkbox"/> Others – Bupropion, Mirtazapine
	Anxiety	<input type="checkbox"/> Optimizing dopaminergic therapy to limit “off” time	<input type="checkbox"/> SSRI <input type="checkbox"/> BZD
	Impulse control disorders - Pathological gambling/ punding	<input type="checkbox"/> Dose reduction or discontinuation of the offending dopamine agonist	<input type="checkbox"/> Dose increase or initiation of levodopa or another PD medication
	Dementia	<input type="checkbox"/> Rule out all other secondary causes like offending anticholinergic agents, depression, etc.	<input type="checkbox"/> Cholinesterase inhibitors – Rivastigmine, Donepezil <input type="checkbox"/> Memantine
	Psychosis		<input type="checkbox"/> Reducing or changing the dopaminergic therapy <input type="checkbox"/> Quetiapine <input type="checkbox"/> Clozapine <input type="checkbox"/> Avoid typical antipsychotics such as haloperidol
Sensory symptoms	Fatigue		<input type="checkbox"/> Modafinil <input type="checkbox"/> Methylphenidate
	Pain		<input type="checkbox"/> Analgesics <input type="checkbox"/> Dopaminergic drugs for non motor fluctuation related pain such as off related dystonic pain <input type="checkbox"/> Baclofen <input type="checkbox"/> Opiates (Tramadol, Oxycodone with naloxone)
Autonomic dysfunction	Orthostatic hypotension	<input type="checkbox"/> Increased salt and water intake <input type="checkbox"/> Waist-high support stockings <input type="checkbox"/> Elevation of head of the bed <input type="checkbox"/> Physical counter manoeuvres	<input type="checkbox"/> Avoid volume depleting drugs (diuretics, <input type="checkbox"/> antihypertensives) <input type="checkbox"/> Avoid Amantadine <input type="checkbox"/> Fludrocortisone <input type="checkbox"/> Ephedrine <input type="checkbox"/> Midodrine
	Sialorrhoea	<input type="checkbox"/> Speech <input type="checkbox"/> Swallowing therapy <input type="checkbox"/> Chewing gum or sucking on hard candy	<input type="checkbox"/> Atropine drops <input type="checkbox"/> Botulinum toxin A and B <input type="checkbox"/> Glycopyrrolate <input type="checkbox"/> Ipratropium bromide spray
	Nausea & Vomiting	<input type="checkbox"/> Initial slow dose titration of dopaminergic agents	<input type="checkbox"/> Domperidone <input type="checkbox"/> Addition of carbidopa to levodopa <input type="checkbox"/> Don't use dopamine antagonists such as metoclopramide and prochlorperazine
	Constipation	<input type="checkbox"/> Lifestyle advise – like exercise <input type="checkbox"/> Fibre-rich diet <input type="checkbox"/> Ensure adequate fluid intake to avoid dehydration	<input type="checkbox"/> Laxatives or stool softeners – Macrogol, Lactulose, Senna <input type="checkbox"/> Avoid constipating opiates for pain
	Bladder dysfunction – urgency, nocturia	<input type="checkbox"/> Eliminate liquids in the evening <input type="checkbox"/> Exercise-based behavioural therapy <input type="checkbox"/> Adjust PD medications to reduce “off” time	<input type="checkbox"/> Anticholinergic agents – Oxybutynin, Tolterodine, trospium chloride <input type="checkbox"/> Desmopressin spray for troublesome nocturia
	Sexual dysfunction (commonly erectile dysfunction)	<input type="checkbox"/> Review all medications including drugs for depression and cardiac problems	<input type="checkbox"/> Phosphodiesterase-5 inhibitors – Sildenafil, Tadalafil, vardenafil
	Thermodyregulation	<input type="checkbox"/> Adjustments to PD medications	<input type="checkbox"/> Botulinum toxin injections may reduce sweating <input type="checkbox"/> Deep brain stimulation
Sleep disorders	Excessive daytime sleepiness	<input type="checkbox"/> Sleep hygiene (regular daytime exercise, avoiding stimulants at bedtime, regular hours of sleep at night)	<input type="checkbox"/> Reduce dopaminergic agents <input type="checkbox"/> Modafinil <input type="checkbox"/> Methylphenidate
	Insomnia/ Fragmented sleep	<input type="checkbox"/> Sleep hygiene	<input type="checkbox"/> Trial of extended-release carbidopa/levodopa or a long-acting dopamine agonist <input type="checkbox"/> Short-acting BZD <input type="checkbox"/> Non-BZD hypnotics – Zopiclone, Zaleplon <input type="checkbox"/> TCA – Amitriptyline, Trazodone <input type="checkbox"/> TCA – Mirtazapine
	REM sleep behavior disorder	<input type="checkbox"/> Safe environment while in bed (remove all sharp and breakable objects)	<input type="checkbox"/> Clonazepam <input type="checkbox"/> Melatonin <input type="checkbox"/> Pramipexole with Clonazepam

BZD - Benzodiazepine; SNRI - Serotonin and norepinephrine reuptake inhibitor; SSRI - Selective serotonin reuptake inhibitor; TCA - Tricyclic antidepressants;

CONCLUSION

The widespread NMS comprise of a variety of cognitive, neuropsychiatric, gastrointestinal, sleep, autonomic, and sensory dysfunctions. They are commonly encountered in PD and are associated with significant morbidity and disability. They are if not more, than equally responsible for detrimental status of health related QoL in patients with PD. The pathological degenerative process in PD not only resides in nigrostriatal region, but also in other cortical and subcortical areas, which lead to cohort of NMS. Many NMS even precede the appearance of classic motor manifestations as a prodrome to the eventual illness. With emergence of better understanding of NMS and motor symptoms, approaches are on way to amend the currently utilized criteria's to diagnose PD. Despite its importance and frequency, NMS are not adequately recognized in clinical practice. This under documented symptomatology needs to be duly addressed in routine clinics, moreover because treatment for many NMS exists with good response that can significantly improve the health related QoL in patients with PD.

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CORRIGENDUM

The article "Analysis of Discriminant Validity of WHOQOL-BREF and Generic health-Related QoL in North Indian Adolescents" with the names of the institutions "¹Symbiosis Institute of Health Sciences (SIU), Pune, Maharashtra, India. ²Department of Hospital administration, Sanjay Gandhi Post graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India", appearing on page 229, JIMSA Oct-Dec 2015 Issue, Vol 28, Vol. 4, the names of the authors were inadvertently missed. The names of the authors of the article are

¹Kasturi Shukla, ²Hem Chandra.

¹Symbiosis Institute of Health Sciences (SIU), Pune 411004, Maharashtra, India

²Department of Hospital Administration, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

The omission of names of authors is extremely regretted.

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