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# Early Parkinson's disease and non-motor issues

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**Abstract** Non motor symptoms (NMS) of PD are a key determinant of health, quality of life and societal cost of PD. Contrary to common perception, many NMS of PD occur early in PD and some may even predate the diagnosis of PD which is based on motor signs. These include olfactory deficit, sleep problems such as REM behaviour disorder, contipation and the more recently described male erectile dysfunction. The non motor quesionnaire (NMSQuest) and the recently validated NMS scale allow falgging and quantification of NMS of PD and therefore are important tools to comprehensively assess symptom load in PD.

**Key words** Non Motor · Parkinson's disease · Olfaction · RBD · Constipation

## Introduction

Non-motor symptoms (NMS) in Parkinson's disease (PD) are common and were recognized by James Parkinson himself. Thus, in his Essay on the Shaking Palsy in 1817, he referred to sleep disturbance, constipation, urinary incontinence and delirium [1]. Numerous studies have now indicated that NMS is an integral symptom complex of PD, affecting memory, bladder and bowel, and sleep among others (Table 1), significantly impair quality of life and may precipitate hospitalisation [2–5].

However, despite their impact, the NMS of PD are not well recognised in clinical practice and one US study reported that existing depression, anxiety and fatigue are not identified by neurologists in over 50 % of consultations, and sleep disturbance in over 40 % [6]. Another recent study attempted to correlate non-motor symptoms in PD at presentation retrospectively after clinico-pathological confirmation of diagnosis [7]. 21 % had NMS at presentation and these included pain, anxiety, urinary dysfunction and depression. Some of these patients were more likely to be misdiagnosed initially and had inappropriate medical interventions.

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 [2, 8].

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 movement behavior 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 2).

Stacy et al. 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 [9]. Recent studies using

**Table 1** The non-motor symptom complex of Parkinson's disease

| |
|---|
| Neuropsychiatric symptoms |
| Depression, apathy, anxiety |
| Anhedonia |
| Attention deficit |
| Hallucinations, illusion, delusions |
| Dementia |
| Obsessional behaviour (usually drug induced), repetitive behaviour |
| Confusion |
| Delirium (could be drug induced) |
| Panic attacks |
| Sleep disorders |
| Restless legs and periodic limb movements |
| REM behaviour disorder and REM loss of atonia |
| Non-REM sleep related movement disorders |
| Excessive daytime somnolence |
| Vivid dreaming |
| Insomnia |
| Sleep disordered breathing |
| Autonomic symptoms |
| Bladder disturbances |
| Urgency |
| Nocturia |
| Frequency |
| Sweating |
| Orthostatic hypotension (OH) |
| Falls related to (OH) |
| Coat hanger pain |
| Sexual dysfunction |
| Hypersexuality (likely to be drug induced) |
| Erectile impotence |
| Dry eyes (xerostomia) |
| Gastrointestinal symptoms |
| Dribbling of saliva |
| Ageusia |
| Dysphagia/ choking |
| Reflux, vomiting |
| Nausea |
| Constipation |
| Unsatisfactory voiding of bowel |
| Fecal incontinence |
| Sensory symptoms |
| Pain |
| Paraesthesia |
| Olfactory disturbance |
| Other symptoms |
| Fatigue |
| Diplopia |
| Blurred vision |
| Seborrhoea |
| Weight loss |
| Weight gain (possibly drug induced) |
| Non-motor symptoms related motor fluctuations |
| Autonomic |
| Cognitive |
| Sleepiness |
| Drug Induced non-motor syndromes: |
| Dopamine dysregulation syndrome |
| Serotonin syndrome |
| Parkinson hyperpyrexia syndrome |
| Drug induced hallucinations and other cognitive problems |

the non-motor questionnaire for PD (NMSQuest) have also highlighted the significant occurrence of a range of 30 different NMS in PD in comparison to an age-matched control group (Fig. 1). A range of non-motor symptoms occurred in PD patients from early to advanced disease, correlating strongly with advancing disease. In particular many NMS such as dribbling of saliva, dysphagia, sexual problems and pain had not been discussed with the doctor before being flagged up by the NMSQuest. The study also highlighted that, irrespective of county of study and disease stage, most PD patients are likely to flag up 9–12 different NMS in the NMSQuest at clinic visit [12]. Additionally, further studies validating the first dedicated scale for 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 [12]. The recently published PDLIFE study reported a serial and progressive deterioration in self reported health status of drug-naïve PD patients who were left untreated by clinicians at 9 and 18 months review [13]. The study has underlined the issue that a decision to delay treatment for PD was probably based on assessment of motor state alone, since analysis revealed major deterioration in several domains of the Parkinson's disease questionnaire (PDQ-39) influenced by non-motor issues.

The traditional view of the pathological process in PD has been challenged by Braak et al. who have introduced the concept of a six stage pathological process, beginning at clearly designated "induction sites" [14, 15].

In Braak stage 1 there is degeneration of the olfactory bulb and the anterior olfactory nucleus and this may explain olfactory dysfunction as a pre-motor NMS. Braak stage 2 reflects progression of the pathological process to the lower brainstem which involves areas mediating NMS such as sleep homeostasis and other autonomic features. Sleep may be affected by abnormalities in the sleep-wake cycle–related pathway mediating thalamocortical arousal while the pedunculopontine nucleus, locus coeruleus, subcoeruleus nucleus and the serotonergic raphe nuclei are also thought to be key areas related

**Table 2** A list of non-motor symptoms suggested as pre-clinical (motor) feature in PD

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

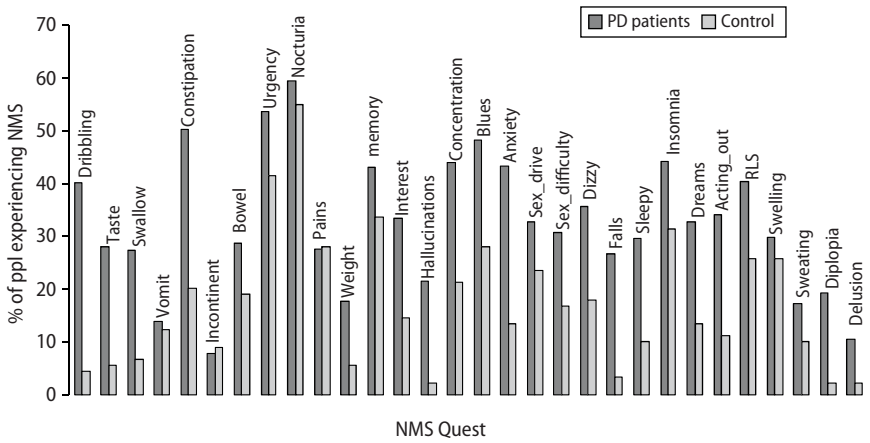


**Fig. 1** NMS as recorded by NMSQuest in control and PD populations (Chaudhuri, et al. (2006) Mov Disord 21(7):916–923)

to the origin of visual hallucinations and rapid eye movement behavioural disorder (RBD) in PD [16–19].

Medullary nuclei also play an important part in central autonomic control while involvement of the dorsal vagal nucleus may explain constipation in PD.

## Olfaction

Olfactory dysfunction (OD) may affect up to 90 % of PD patients and in 1975, Ansari and Johnson suggested the association between olfactory dysfunction and development of PD and subsequently several other workers have established OD as a preclinical marker for PD [20–25, 52] .

Studies have also reported olfactory deficits in asymptomatic relatives of patients with PD, some of whom subsequently became symptomatic [52]. A relationship of lifetime caffeine intake (low intake = higher risk) of olfactory problems and future risk of PD in relatives of cases has been reported [52]. A longitudinal study of 2,263 elderly men between 1991–1996 by Ross and colleagues assessed olfaction using a 12 odour smell identification test and reported an association between impaired olfaction and incident PD [23]. Both olfactory dysfunction and RBD have been reported in other disorders with abnormal synuclein pathology such as diffuse Lewy body disease (LBD) and multiple system atrophy (MSA). Non-synucleinopathies, such as vascular parkinsonism, corticobasal degeneration, progressive supranuclear palsy and *parkin*-associated PD, tend to have intact olfactory function [26]. Hyposmia however, appears to be common in genetic PD associated with the LRRK 2 mutation [27] and also in community dwelling elderly people with mild parkinsonian signs [28]. Rhinorrhoea appears to be common in early PD and it has been suggested that this may confound data related to olfactory dysfunction [29].

Lerner and Bagic have proposed that the pathology of PD may involve a pathogen which causes an anterograde spread from the olfactory bulb and nucleus through the primary, secondary and tertiary connections of the olfactory structures [53]. This may involve intranasal and intrabulbar inoculation of neurotropic viruses such as herpes simplex virus type 1 and mouse hepatitis virus strain JHM. Additionally, a prion like nature of PD has also been posited by the same authors [53].

## REM sleep behaviour disorder (RBD)

RBD is a parasomnia affecting REM sleep characterised by loss of the normal skeletal muscle atonia during REM sleep, thus enabling patients to physically enact often vivid and unpleasant dreams [30, 31].

Like constipation and olfactory disturbance, RBD may precede the development of the motor signs of PD and data would suggest that RBD may precede the onset of motor symptoms in over 40 % of PD patients [2, 30]. Imaging studies in patients with isolated RBD, have indicated a small but significant symmetrical reduction in striatal dopaminergic uptake, which may be suggestive of preclinical PD and more recently patients with RBD has been studied with a combined approach using olfactory testing, transcranial ultrasound and FP-CIT imaging [32–34].

Uchiyama and colleagues reported an autopsy proven case with the presence of incidental striatal Lewy bodies in a patient with RBD for 20 years but no clinical evidence of PD [35]. It is suggested that that RBD may arise due to the degeneration of lower brainstem nuclei including the pedunculopontine and subcoeruleal nucleus areas affected in Braak stages 1 and 2 [36].

The co-occurrence of sleep disturbances and olfactory deficit in PD can be explained by Braak's hypothesis and in a community based study, Henderson et al reported that more patients with olfactory deficits than controls had excessive daytime somnolence (45 % *v* 6 %), restless legs (50 % *v* 19 %), abnormal movements during sleep (34 % *v* 0 %) and these generally occurred three to

five years after diagnosis and were independent of mood disorders and drug therapy [37].

## Constipation

Gastrointestinal symptoms are common in PD and many such as dysphagia, dribbling of saliva, oesophageal dysmotility can occur in advanced PD. Constipation is a common NMS of PD and may precede development of PD [38]. Abbott et al. reported a prospective study which followed the bowel habits of 7000 men for 24 years and reported that those with initial constipation (< 1 bowel movement/day) had a threefold risk of developing PD after a mean interval of 10 years from initial constipation [38]. Involvement of the dorsal vagal nucleus, as would occur in Braak stage 1 may explain the pre-motor appearance of constipation [36]. However, a study by Benarroch et al. show that there appears to be no correlation between the degree of cell loss or Lewy body counts in the dorsal vagal nucleus and the severity of constipation in PD [49]. In PD, there is severe loss of both central and colonic dopaminergic neurons although constipation in PD does not respond well to dopaminergic treatment. Cersosimo and Benarroch have recently reviewed the neural control of the gastrointestinal system in PD and have proposed early involvement of the dorsal vagal nucleus and also the intrinsic neurons of the enteric nervous system in PD [54].

## Depression

In PD, depression can affect up to 10–45 % of PD patients and PD-associated depression may in part arise as a result of damage to serotonergic neurotransmission as well as limbic noradrenergic and dopaminergic mechanisms [39, 40].

Studies have suggested that symptoms of depression may precede the development of PD and as per Braak this may correspond to stage 2 when locus cerulius is involved. In a comparative study of PD and dystonia patients, Lauterbach et al. reported that PD patients more often had a primary diagnosis of simple phobia and a secondary atypical depression (preceding PD) [41].

In a large study, Nilsson et al. reported that depressed patients are more likely to develop PD than osteoarthritis or diabetes while a retrospective cohort study reported that at the time of diagnosis of PD, 9.2 % had a lifetime diagnosis of depression compared to 4.2 % in the controls [42, 43].

Early onset PD patients with Park 2 mutation may have a genetic predisposition to the development of more severe neuropsychiatric symptoms including depression.

## Autonomic dysfunction

Sexual dysfunction in PD may be part of autonomic dysfunction and testosterone deficiency has been implicated [44]. In a prospective study, Gao et al. have reported that men with erectile dysfunction before 1986 were 3.8 times more likely to develop PD during the follow-up than were those without (relative risk = 3.8, 95 % confidence interval: 2.4, 6.0; $P < 0.0001$) [45].

Although, troublesome dysautonomia is recognised in advanced PD, cardiac MIBG imaging demonstrates early cardiac sympathetic denervation in PD (low cardiac uptake) and not MSA where the heart is usually visualised [46]. Cardiac sympathetic denervation has also been linked to genetic forms of PD with alpha synuclein mutation [47, 50]. Recently, Fujishoro and colleagues have reported that cardiac sympathetic denervation in PD correlates with clinical and pathological stages of PD as demonstrated by tyrosine hydroxylase immunoreactivity and propose that cardiac sympathetic denervation may occur in the pre-clinical, pre-motor phase of PD [55].

## Excessive daytime sleepiness

Excessive daytime sleepiness (EDS) affects up to 50 % of PD patients and may also be preclinical marker for PD [48]. The suprachiasmatic nucleus (SCN) regulates the internal rhythm between the two switches (flip-flop switch) while hypocretin (orexin), a hypothalamic peptide may also have a regulatory role. Neuronal degeneration within these areas, involved in Braak stages 1 and 2 may explain the early occurrence of EDS. Sleep studies in untreated PD cases have suggested that nocturia, sleep maintenance insomnia, restless legs syndrome, lack of sleep refreshment, and daytime somnolence can occur even at an early untreated stages of PD [51].

In summary, non-motor symptoms are an integral part of PD and emerge not only at moderate to advanced PD but also in very early PD. A growing body of research also has now established the importance of some of these symptoms as a marker of pre-clinical and pre-motor PD.

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