Non-motor Symptoms in Parkinson's Disease

Ergun Y Uc,[1] Jon Tippin,[1] Kelvin L Chou,[2] Bradley A Erickson,[3] Kevin C Doerschug[4] and Decontee M Jimmeh Fletcher[5]

1. Associate Professor, Department of Neurology, University of Iowa, and Neurology Service, Veterans Affairs Medical Center, Iowa City; 2. Clinical Associate Professor, Departments of Neurology and Neurosurgery, University of Michigan; 3. Assistant Professor, Department of Urology, University of Iowa; 4. Associate Professor, Department of Internal Medicine, University of Iowa; 5. Assistant Professor, Department of Neurology, University of Iowa, and Neurology Service, Veterans Affairs Medical Center, Iowa City

Abstract

In addition to typical motor dysfunction (parkinsonism), diverse non-motor symptoms (NMS) are frequently observed in patients with Parkinson's disease (PD). Some NMS may antedate the diagnosis of PD. Examples of NMS include cognitive impairment, autonomic dysfunction, visual dysfunction, sleep abnormalities and psychiatric disorders. NMS are associated with wide-ranging abnormalities in extranigral dopaminergic systems and non-dopaminergic (e.g. cholinergic, noradrenergic, serotoninergic) systems. The type and severity of NMS vary based on age, disease severity and predominant motor symptoms. NMS can be disabling and reduce quality of life. Treatment of NMS can be challenging. Some NMS are helped by dopaminergic treatment, whereas others can be induced or exacerbated by treatments that help the motor dysfunction. Physicians should probe their PD patients about their NMS and address them for better care. Clinical trials should incorporate NMS as outcomes for more meaningful conclusions on the effect of treatments under investigation.

Keywords

Parkinson's disease, cognition, dementia, vision, constipation, autonomic dysfunction

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Correspondence: Ergun Y Uc, Department of Neurology, University of Iowa Carver College of Medicine, 200 Hawkins Drive-2RCP, Iowa City, IA 52242, US. E: ergun-uc@uiowa.edu

The degeneration of the dopaminergic nigrostriatal system and parkinsonism (rest tremor, rigidity, bradykinesia and postural instability/gait disorder) represent only one aspect of Parkinson's disease (PD), a multifaceted and complex disorder.[1] In addition to this typical motor dysfunction, non-motor symptoms (NMS) also significantly reduce of quality of life.[2–4] Several non-motor features are associated with deficits in extranigral dopaminergic pathways (e.g. mesolimbic, mesocortical), while others involve non-dopaminergic systems in the nervous system (e.g. cholinergic, noradrenergic, serotoninergic).[5] Sleep (e.g. rapid eye movement behaviour disorder), olfactory and autonomic dysfunction (e.g. constipation) may precede the onset of parkinsonism by many years,[1,6] consistent with the debated notion that PD pathology starts in the lower brainstem and that midbrain (i.e. nigral) involvement represents stage three out of six pathological stages.[7] Considering parkinsonism as just the tip of the iceberg of a multifaceted and complex disorder, PD might be better viewed as a 'centrosympathomyenteric neuronopathy,' as per Langston.[1] In this article, various non-motor aspects of PD (see *Table 1*) are discussed.

Cognition

Cognitive impairment can be present in the early,[8,9] even yet untreated[10] stages of PD. Cognitive impairment is associated with poorer quality of life[11] and reduced activities of daily living (e.g. worse driving[12–15])[9] and increases cost of care in PD.[16] Dementia in PD is an important risk factor for nursing home placement and death.[17,18] Depending on the baseline age, severity of parkinsonism, cognitive function and setting (hospital versus community based) of the studied population, 20–83 % of PD patients develop dementia.[19–25] About one-quarter of PD patients without dementia have mild cognitive impairment (PD-MCI),[26,27] which is shown to be present in approximately 20 % at time of diagnosis.[28] The typical cognitive deficits in PD include visuospatial, attentional and executive deficits, but memory deficits are also present.[29] Cognitive impairment in PD is associated with limbic and cortical Lewy bodies, amyloid plaques and central cholinergic deficits in addition to dysfunction of dopaminergic frontostriatal circuits.[29] Risk factors for dementia include postural instability and gait difficulty, bulbar dysfunction, hallucinations, advanced age, male gender, depression, autonomic dysfunction and poor performance on baseline cognitive tests.[20,21,30–32] PD-MCI predicts a shorter time to dementia.[26]

Dopaminergic medications have mixed effects on cognition. They can improve or impair cognitive performance depending on the nature of the task and the basal level of dopamine function in the underlying corticostriatal circuitry.[33] For example, task switching (which is dependent on circuitry connecting the dorsolateral prefrontal cortex and the posterior parietal cortex to the dorsal caudate nucleus) improved, but probabilistic reversal learning (which is dependent on orbitofrontal cortex–ventral striatal circuitry) deteriorates with use of dopaminergic medications.[33] While deep brain stimulation (DBS) of the subthalamic nucleus greatly improves motor function and overall quality of life, a mild decline in various cognitive functions (e.g. verbal fluency, information processing) has been observed.[34–36] Randomised controlled trials have shown modest benefits for central acetylcholine esterase inhibitors[37] (e.g. rivastigmine,[38] donepezil[39]) and memantine[40,41] in PD dementia. There are currently no systematic clinical trials in PD-MCI.[29] Behavioural treatment options (e.g. cognitive behavioural therapy, exercise) are under investigation.

Table 1: Classification of Non-motor Symptoms in Parkinson's Disease by System or Function

Cognition
Domains
• Executive dysfunction • abnormalities in attention
• visuospatial abnormalities • memory loss
Stages
• Mild cognitive impairment • dementia
Vision
• Reduced contrast sensitivity and acuity • reduced spatial and motion perception • reduced processing speed and attention
• reduced visuoconstructional abilities
Psychiatry
• Depression • anxiety • psychosis • impulse control disorders • apathy
Gastroenterology
• Constipation • delayed gastric emptying
Cardiovascular System
• Orthostatic hypertension • cardiac denervation
Genito-urinary System
• Urinary urgency and incontinence • erectile dysfunction
Respiratory System
• Abnormal breathing • aspiration
Sleep
• Sleep fragmentation • restless leg syndrome and periodic limb movements of sleep • obstructive sleep apnoea • excessive daytime sleepiness
• rapid eye movement (REM) sleep behaviour disorder
Others
• Weight loss • loss of smell

Vision

PD affects visual function across all levels: ocular,[42] basic sensory functions (visual acuity, colour vision, contrast sensitivity), perception (information processing speed, attention, spatial orientation, motion perception) and higher functions (cognitive level) such as non-verbal memory and construction.[9,43–45] Visual perception and cognition abnormalities are associated with dysfunction ranging from retinal to cortical levels.[17] Visual dysfunction is associated with gait and balance impairment and visual cues can improve freezing of gait.[46–48] Driving is a primarily visual task and visual function deficits at different levels are important risk factors for unsafe driving and driving cessation in PD.[14,15,49]

Psychiatry

Depression

Depression is the most common neuropsychiatric disturbance seen in PD.[50] It may present at any time and contributes to decreased quality of life.[51] The prevalence of depression ranges from 2.7 to 90 %, depending on how it is defined.[52] In a recent systematic review, the weighted prevalence of major depressive disorder in PD was 17 %, minor depression was 22 %, and dysthymia was 13 %.[52] Depression may be difficult to recognise in PD because of commonly shared features, such as blunted facial expression, psychomotor slowing, appetite changes, fatigue and sleep disturbances. Women, those with a family history of depression and those with other psychiatric co-morbidities (anxiety, apathy, etc.) may be at higher risk of developing depression.[53–55] Limited randomised trials exist to guide treatment for depression in PD. In randomised, placebo-controlled trials of antidepressants in PD, the tricyclics nortriptyline and desipramine have been demonstrated to improve depressive symptoms compared with placebo, whereas selective serotonin re-uptake inhibitors (SSRIs) have not been found to be as effective.[56,57] Despite this, most PD patients with depression are generally prescribed an SSRI,[58] likely because of its adverse effect profile. Pramipexole, used to treat motor symptoms in PD, also appears to have an antidepressant effect.[59]

Anxiety

Anxiety is estimated to occur in up to 40 % of patients with PD.[60,61] Similar to depression, the presence of anxiety is associated with a worse quality of life.[60] Panic disorder and generalised anxiety disorder have been reported to be the most common anxiety syndromes in PD, but a recent study demonstrated that anxiety disturbances in PD tend not to fall into discrete subtypes.[60] Very little is known about the pathophysiology of anxiety in PD. Anxiety is highly associated with 'on–off motor fluctuations in PD, with worsened anxiety and panic attacks during 'off' periods and improvement during 'on' states.[62] Although the exact underlying mechanism for this is unclear, patients may experience anxiety because of the immobility associated with 'off' periods. There are no randomised controlled trials of anxiety agents in the PD population. In the general population, antidepressants and benzodiazepines have shown to be beneficial. If the anxiety seems to occur only with wearing off, adjusting PD medications to prolong 'on' times may be helpful.

Psychosis

Psychosis is estimated to occur in 20–40 % of PD patients, usually in the advanced stages of the illness.[50,63] It is the single greatest risk factor for nursing home placement in patients with PD and contributes to caregiver stress.[64] The most common manifestations of psychosis in PD are visual hallucinations.[63,65] Non-visual hallucinations (auditory, tactile, olfactory) and delusions may also be present, though less frequently.[65] Advanced age, impaired vision, depression, sleep disorders and longer disease duration are associated with the development of psychosis in PD.[66] Psychosis can occur with all of the antiparkinsonian medications. The pathophysiology of psychosis in PD is poorly understood and may be attributable to hypersensitisation of dopamine receptors in the mesolimbic/mesocortical pathways. Serotonin may also be involved since the atypical antipsychotic drugs are purported to work through their high affinity for serotonin receptors. The first step in managing PD psychosis is to treat any reversible causes, such as infection, metabolic derangements, social stress and drug toxicity. After that, antiparkinsonian medications should be reduced and discontinued if possible. If psychosis persists, the use of an atypical antipsychotic agent is warranted. A recent American Academy of Neurology guideline looked at the evidence behind atypical antipsychotics for the treatment of psychosis in PD and recommended clozapine (level B) and quetiapine (level C).[67] Although there are stronger data for the efficacy of clozapine for PD psychosis, it is used rarely in practice because of the concern for agranulocytosis and mandated blood monitoring. As a result, quetiapine is typically used first and, if it is not helpful, clozapine is then substituted. Olanzapine may worsen motor function in PD.

Impulse Control Disorders

Impulse control disorders (ICDs), such as pathological gambling, excessive shopping, overeating, hypersexuality and excessive dopaminergic medication use, are estimated to occur in up to 14 % of treated PD patients.[68] These behaviours are associated with dopaminergic replacement therapies, especially dopamine agonists and may result in devastating consequences for patients and their families. Younger patients, patients with a history of smoking or substance abuse problems and patients with a family history of gambling problems are at greater risk for developing ICDs.[68,69] ICDs in patients with PD are also associated with more depressive and anxiety symptoms, increased obsessionality, more novelty seeking behaviour and higher levels of

impulsivity.[69] The 'overdose' theory has been proposed to explain the presence of ICDs in PD. Because the ventral striatum (associated with cognitive and limbic pathways) is relatively preserved in PD compared with the dorsal striatum (associated with motor dysfunction), there may be a relative 'overdosing' of dopamine in the ventral striatum that results in these ICDs when dopaminergic treatment is initiated for motor symptoms.[70] Ideally, when an ICD is present, the dopamine agonists should be reduced and discontinued; however, patients often do not tolerate this because of motor worsening. Subthalamic nucleus DBS has been proposed as a way of treating ICDs[71] because it allows a reduction in medication doses while helping motor symptoms, but ICDs have been reported to occur after DBS surgery.[72] A recent double-blind cross-over study reported that amantadine could improve pathological gambling in PD,[73] but it is unclear if all ICDs are helped by this medication.

Apathy

Apathy is defined as a loss of motivation, interest and effortful behaviour.[74] Although apathy frequently occurs in conjunction with depression, it can occur independently in PD.[74] Approximately 50 % of PD patients may develop apathy.[74,75] Dementia and axial motor decline appear to be risk factors[75] and increased apathy has been reported post-DBS surgery.[76] The neurological basis of apathy is most commonly ascribed to frontal lobe dysfunction. Apathy is difficult to treat and often bothers caregivers more than the patient. Unfortunately, there are no effective treatments for apathy in PD.

Gastroenterology

Constipation occurring as early as 20 or more years before the onset of motor symptoms is associated with an increased risk of PD.[77] Constipation is common in PD; many patients need oral laxatives and 7 % of PD patients meet criteria for severe constipation, which is associated with disease duration and severity.[78] Constipation is one of the most important predictors of nutritional impairment in PD.[78] Early gastrointestinal symptoms predict future cognitive impairment in PD.[79] Delayed gastric emptying with solids is seen in 60–90 % of PD patients and is associated with the severity of parkinsonism,[80,81] even though it is also seen often in early stages of the disease.[82] Abnormal gastric emptying can affect motor symptom control adversely by leading to unpredictable fluctuations in the levels of dopaminergic drugs.[83]

Lesions similar to the ones observed in the brain have been identified in the submucosal plexus of the enteric nervous system on routine colonic biopsies of PD patients.[84] In addition to the fact that constipation is associated with future risk of PD and with incidental Lewy bodies in the locus ceruleus or substantia nigra, constipation is associated with low substantia nigra neuron density even in people without PD independent of the presence of incidental Lewy bodies (suggesting a pre-diagnostic stage of PD).[85] The most likely causes of constipation and gastric emptying problems in PD are degenerations of the dorsal vagal nucleus and the intramural plexus of the whole intestine, which probably develop prior to the degeneration of dopaminergic neurons of the substantia nigra.[83] Animal models of PD (transgenic mice,[86,87] 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP]-treated monkeys,[88] rats with unilateral 6-hydroxydopamine lesion of nigrostriatal dopaminergic neurons,[89] rotenone-infused rats[90]) show abnormalities in gastrointestinal motility, clinical, and electrophysiological features, and pathological findings in the enteric nervous system, which are similar to human disease.[91]

Treatment of constipation is usually unsatisfactory despite multiple interventions (dietary modification, bulk-forming agents, stool softeners, and laxatives).[92] Preliminary studies suggested benefits for constipation using tegaserod,[92,93] isosmotic macrogol electrolyte solution,[94] or subthalamic nucleus DBS.[95] A preliminary study showed potential benefit from mosapride on shortening gastric emptying half-time with a concomitant decrease in motor response fluctuations.[96]

Cardiovascular System

Orthostatic hypotension is frequent in PD and can increase susceptibility to disabling falls and life-threatening injuries. The mechanism of sympathetic neurocirculatory failure in PD is not clear. However, Lewy bodies are observed in both central and peripheral autonomic pathways.[97] Norepinephrine is decreased in the post-ganglionic region in the sympathetic nervous system, especially in the heart. Abnormal physiological reflexes also contribute to orthostatic hypotension. In normal individuals, the cardiovagal baroreceptor reflex refers to the change in R-R interval (interval between successive R waves on electrocardiogram) per unit change in systolic blood pressure. This reflex is known to contribute to the beat-to-beat control of arterial blood pressure. Also, with Valsalva manoeuvre, the increased intrathoracic pressure leads to reduced venous return, stroke volume and cardiac output. These physiological changes stimulate a sympathetic response that releases norepinephrine at the sinoatrial node, thereby increasing heart rate. Both of these sympathetically driven reflexes are blunted in PD patients with or without orthostatic hypotension.[98] To complicate the issue further, levodopa therapy can induce hypotension through its diuretic and naturetic properties. Low-dose dopamine stimulates vascular smooth-muscle cell receptors to cause vasodilatation. However, Goldstein and colleagues demonstrated that orthostatic hypotension in PD is independent of levodopa therapy.[99] This is thought to be attributable to the underlying sympathetic deregulation in the overall disease process.

The combination of orthostatic hypotension and parkinsonism is often misdiagnosed as multiple system atrophy (MSA). However, MSA is distinguished from classic PD by intact sympathetic cardiovascular innervation. Studies with radioactive imaging agents, such as I-123metaiodobenzylguanidine and 6-fluorodopamine, show decreased uptake in the myocardium of PD patients regardless of the clinical presence of orthostatic hypotension.[99] Work by Senard et al. revealed that mean plasma norepinephrine is lower in PD patients, suggesting the possibility of a more generalised sympathetic denervation.[100] Current conservative treatment includes increasing fluid intake, a high-salt diet, and high-compression stockings. If post-prandial hypotension is an issue, small and frequent meals can be helpful. Medications used include fludrocortisone and the selective alpha-1 agonist midodrine. Midodrine is currently on the market, but new studies may be needed for continued approval. Chronic sympathetic denervation can lead to supersensitivity to adrenoreceptor agonists, exacerbating supine hypertension. Pyridostigmine is a more favourable therapy owing to avoidance of this adverse effect, yet it is a less effective therapy.[98]

Genito-urinary System

Lower urinary tract symptoms (LUTS) affect 35–70 % of patients with PD, with most studies showing a correlation with the severity of the overall disease.[101–103] These rates tend to be lower if MSA has been carefully eliminated from the study population, as LUTS are found in nearly all MSA patients.[104] The most widely accepted theory explaining LUTS pathogenesis in PD is that the loss of basal ganglia neurons disrupts normal inhibition of the micturation reflex (located in the pontine micturation centre), mediated by D1 receptors.[105] This loss of reflex

inhibition leads to an unstable bladder, resulting in the urgency and frequency symptoms most often described by PD patients. This theory is supported by reports of improved LUTS after DBS of the subthalamic nucleus.[106] The degree of cell degeneration has been shown to correlate with the severity of symptoms.[107] Storage symptoms (urgency, frequency, nocturia) are more common than voiding symptoms (straining, hesitancy) in PD patients with LUTS. The most common symptom is nocturia, with over 60 % of PD patients reporting having to urinate more than two times per night.[108,109] However, the overlap of nocturia and primary sleep disturbances in PD patients makes it a difficult symptom to both follow and treat.[107] Urinary urgency is reported in 33–54 % of PD patients.[101] Voiding symptoms are found more often in older males, corresponding with the age-related growth of the prostate.[101] Urodynamic studies (UDS) can add significant value in the evaluation of LUTS in PD patients, giving information such as bladder volume, sensitivity, post-void residuals, presence/absence of incontinence and storage pressures. Additionally, when trying to differentiate between PD and MSA, MSA patients are much more likely to have large post-void residuals, an open bladder neck and detrusor–sphincter dyssynergia on UDS than those with PD.[104] Information from UDS can be especially useful when directing treatment in refractory disease.

All PD patients with LUTS should have a bladder infection ruled out before initiating treatment. Behavioural modification, including decreasing evening fluid intake to decrease nocturia and timed voiding to minimise daytime urgency and urge incontinence, should be initiated in all PD patients with LUTS. PD medications, such as levodopa, have been shown to affect bladder function, although there are conflicting reports as to whether they improve or worsen symptoms.[102,110] In general, these medications should not be considered as a primary treatment for *de novo* LUTS in PD patients.

Anticholinergic medications are considered first-line treatment for storage symptoms in PD patients. These medications act on the parasympathetic nervous system in the bladder via the M_3 receptors, and have been shown to decrease both the number of voids over 24 hours and the frequency of nocturia and urge incontinence through their inhibitory effect on the bladder wall smooth muscle.[111] However, use of anticholinergic medication in PD patients, especially in elderly patients, has been linked to cognitive impairment, so the benefits of the medications must be weighed against these potential adverse effects. It is possible that more selective anticholinergics that do not cross the blood–brain barrier will improve their adverse effect profile.[112,113] Other medications such as diazepam, baclofen, duloxetine, and dantrolene may improve symptoms via effects on external sphincter and bladder sensation.[114] Desmopressin can decrease isolated nocturnal polyuria in PD patients with disrupted circadian vasopressin rhythms.[108]

Neuromodulation of the sacral nervous input to the bladder offers a promising surgical intervention for refractory LUTS in PD patients. Surgical modulation is thought to override the altered central micturation reflex and co-ordinate voiding. Cystoscopic injection of botulinum toxin into the detrusor muscle of the bladder is another promising therapy that can improve bladder capacity and decrease urgency and incontinence episodes in PD patients.[115]

Respiratory System

Most patients with PD report breathlessness.[116] The aetiology of this symptom is likely multifactorial, including dysfunctions of the upper airway, respiratory muscles and lung parenchyma. Diaphragm muscle function is likely preserved in PD. However, electromagnetic studies demonstrate clear abnormalities in the function of accessory muscles of respiration. Specifically, scalene and intercostal muscle tremor and tone serve to counteract the negative inspiratory pressure initiated by the diaphragm.[117] These counteracting forces may result in net reduction of change in pleural pressure and the appearance of respiratory muscle weakness. Indeed, reduced inspiratory flow rates, and in some patients evidence of restrictive physiology, are identified upon pulmonary function testing. Upper airway dysfunction also occurs owing to tone and especially tremor of muscles controlling the glottis. This leads to airway obstruction of passive exhalation, the physiological importance of which is variable. In general, the forced expiratory volume in one second is preserved in PD, although flow volume loops from spirometry may demonstrate the reduced flows consistent with variable (not fixed) upper airway obstruction.[118]

Inadequate glottis control can lead to recurrent microaspiration, which can further impair lung parenchymal function. Cough strength is generally low, impairing the ability to remove aspirated secretions and food particles. In addition to microaspiration, aspiration pneumonia is the leading cause of death in PD. Expiratory muscle strength training can increase cough strength independent of other respiratory parameters,[119,120] although whether this affects the incidence or severity of aspiration has not yet been tested. Independent of pulmonary function, patients with PD may have reduced co-ordination between breathing and locomotion.[121] It is therefore plausible that breathing during activities of daily living is less efficient, thus contributing to a feeling of breathlessness. Despite these potential barriers owing to abnormal respiration, patients with mild to moderate PD are reliably able to exercise to maximum intensity and achieve peak oxygen consumption and workloads that are similar to age-matched controls.[118,122] However, unlike healthy controls who terminate maximum exercise owing to muscle fatigue, PD patients are more likely to terminate exercise owing to breathlessness.[118] Accordingly, mild to moderate PD patients likely can participate in aerobic exercise programmes and might be offered the same cardiovascular, metabolic and psychological benefits as individuals without PD.

Sleep

Sleep Fragmentation

Most patients with PD will have disturbed nocturnal sleep at some point during the course of their disease and for about one-third of them it is considered a moderate to severe problem.[123] Sleep disturbances worsen as PD progresses, and become more common in patients with higher Hoehn and Yahr stages.[124] Sleep fragmentation – that is, a lack of sleep continuity owing to frequent awakenings – is the most common complaint for these patients in this regard. Fragmented sleep may be caused by a concomitant sleep disorder, such as obstructive sleep apnoea (OSA) (see below) or nocturia, but a return of PD motor symptoms or medication effects is often at fault.[125] Recurrence of tremor or the inability to turn over in bed most often occurs in light non-REM sleep (N1, N2), thereby leading to difficulty initiating sleep or re-initiating sleep after an awakening. Treatment with levodopa, as well as implantation of a deep brain stimulator, has been shown to improve these troubling symptoms.[126,127] On the other hand, dopamine agonists can actually potentiate nocturnal motor activity and lead to resultant sleep fragmentation in some patients.[128,129] In those who are disturbed by increased dyskinesias, nightmares and hallucinations, a reduction in evening medication doses may be helpful.

Restless Leg Syndrome and Periodic Limb Movements of Sleep

Restless leg syndrome (RLS) and the related periodic limb movements of sleep (PLMS) can cause sleep-onset insomnia or sleep fragmentation, and have been found by some authors to be increased in PD patients.[130,131] While it is tempting to think that RLS would naturally be increased in PD because both conditions are attributable to a dopaminergic deficiency state and respond to levodopa or dopamine agonists, it is likely that dopaminergic pathways other than the nigrostratal system (which is central to PD) are involved in RLS.[132] Moreover, the association between RLS/PLMS and PD may not necessarily implicate a common pathophysiology, but rather reflect distinct processes that are more common in older individuals (e.g. iron deficiency, use of antidepressants). Regardless, the common responsiveness to dopaminergic therapy allows for treatment of both conditions in co-morbid individuals with the same or similar treatment regimens.

Obstructive Sleep Apnoea

OSA has been claimed to be more frequent in PD than in the general population in some studies[133] but not in others.[134] Again, as the number of obstructive apnoeas and hypopnoeas per hour of sleep increase with age,[135] the purported association between PD and OSA may only reflect conditions that are more common with advancing age. Nevertheless, like most patients with OSA, many of those with PD have excessive daytime sleepiness (EDS), which may raise clinical concern for OSA in these individuals. In point of fact, more than 15 % of PD patients, compared with 4 % of age-matched controls with diabetes, have EDS.[123,136] EDS in these patients is correlated with PD severity, cognitive decline, and longer use of levodopa and dopamine agonists.[137–139] Although agonists have been considered to be a major cause of EDS and 'sleep attacks,' it appears that the total load of both types of medications leads to excessive sleepiness in susceptible patients.[140] While the previously described sleep fragmentation would be expected to cause daytime sleepiness, some investigators have failed to find that it is a major cause of EDS in PD compared with age-matched controls.[136] Of interest, a narcolepsy-like state, complete with sleep-onset REM periods and short mean sleep latency on the multiple sleep latency test, has been found to cause EDS in some PD patients. Unlike typical narcolepsy, cataplexy is not seen in these PD patients.[141] Management of EDS includes excluding other causes, such as depression, decreasing or changing levodopa/dopamine agonists and using stimulants such as modafinil.[142] It is important to recall that depression is much more common in PD than in the general elderly population[52] and EDS (as well as insomnia) is a common clinical feature in affected individuals. Regardless of the cause, sleepy drivers with PD have an increased crash risk and should be restricted from driving until effectively treated.[143]

Rapid Eye Movement Sleep Behaviour Disorder

REM sleep behaviour disorder (RBD) is characterised by increased EMG activity and dream enactment behaviour during REM, when atonia usually renders individuals motionless. RBD is not only common in PD, perhaps affecting as much as 50 % of this population, but may be a harbinger for the later development of PD or other synucleinopathies in otherwise asymptomatic individuals.[144] RBD has been shown to antedate the onset of PD by as much as 50 years in some patients and its presence increases the likelihood of the later development of dementia.[145] As in patients with idiopathic RBD, affected PD patients can often be treated successfully with clonazepam, and there are reports that donepezil, melatonin and pramipexole may also be helpful.[146–148] Similar to RLS/PLMS, RBD may be caused or aggravated by antidepressants,[149] a fact that should be borne in mind by clinicians. As with any patient suffering from RBD, making the sleeping environment safe and protecting bed partners from inadvertent injury are of paramount importance.

Others

Weight loss is frequently observed in PD and is associated with severity of parkinsonism, hallucinations, cognitive decline, and eating and swallowing difficulty.[150–155] Successful DBS treatment is associated with weight gain.[156,157] Loss of smell is frequent in PD, as in other neurodegenerative disorders (e.g. Alzheimer's disease) and may antedate the diagnosis by many years.[158] Olfactory dysfunction in PD has been linked to cholinergic denervation of the limbic archicortex and may be a risk factor for cognitive impairment.[159]

Conclusion

NMS of PD are diverse, frequent and disabling. Although they have been underappreciated and under-researched for decades,[160] there is increased awareness of their presence and importance. There are now validated clinical and research tools such as the NMSQuest, the NMS scale, the Scales for Outcomes in Parkinson's disease (SCOPA), and the modified version of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) for assessing NMS.[160] Physicians should probe their PD patients about their NMS and address them to improve their quality of life. Clinical trials should incorporate NMS as outcomes for more meaningful conclusions on the effect of treatments under investigation. Primary research on NMS will improve the understanding of PD and will advance the care of PD patients. ■

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