Review Article

Parkinson’s disease: more than a movement disorder

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Abstract

The classical motor symptoms of Parkinson’s disease have long been recognized, studied, and researched. Recently, more interest is shown in non-motor symptoms of Parkinson’s disease due to their impact on patients’ quality of life (QOL). They usually dominate the advanced stages of Parkinson’s disease, but can as well predate the motor symptoms.

Awareness of physicians with these symptoms is needed, not only for early intervention to avoid their negative impact on QOL, life expectancy, but these symptoms may also give clues to early diagnosis of Parkinson’s disease in at risk population.

Keywords: Parkinson’s disease, non-motor symptoms, sleep disorders

Introduction

The diagnosis of Parkinson’s disease (PD) has long been based on its motor features. Bradykinesia, rigidity, tremors and postural instability are the corner stones for the diagnosis of PD. These motor symptoms of PD are extensively studied and researched resulting in better understanding of its pathophysiology, improved diagnostic accuracy and development of robust rating scales and treatment strategies.

Recently, more attention and emphasis is shifting towards highlighting the non-motor symptoms (NMS) of PD. Indeed, these symptoms dominate the clinical presentation of late stages PD, but can of course predate the diagnosis of PD. They remain poorly understood compared to the motor symptoms, directly resulting from dopamine deficiency, as a consequence of degeneration of the substantia nigra.

The understanding and recognition of these symptoms is of paramount importance since they contribute to poor quality of life, severe disability and even shortened life expectancy.

Scale of the problem

Large range of symptoms comprises the NMS of PD (Table 1).

The prevalence of NMS as a whole is inadequately documented due to lack of community powered based studies on prevalence, effect and treatment.

NMS of PD such as bowel and urinary symptoms, sleep disorders and erectile impotence might not be brought to the attention of health care professionals. This is because patients are embarrassed or unaware that these symptoms are linked to PD. This
under recognition of these symptoms can have social and therapeutic implications as these symptoms can adversely progress if left untreated, further worsening the quality of life. This can also lead to frequent hospitalization and institutionalisation increasing the cost of care for these patients\(^2\).

Table 1: Non-motor symptoms of PD

<table>
<thead>
<tr>
<th>Neuropsychiatric symptoms</th>
<th>Depression, apathy, anxiety, anhedonia, hallucinations, illusions delusions, dementia, obsessional behaviour, confusion, panic attacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep disorders</td>
<td>Restless leg syndrome and periodic limb movement, rapid eye movement (REM) sleep behaviour disorder and REM loss of atonia, non-REM-sleep related movement disorders, excessive daytime somnolence, vivid dreaming, insomnia, sleep disordered breathing</td>
</tr>
<tr>
<td>Autonomic symptoms</td>
<td>Bladder disturbances, urgency, nocturia, frequency, sweating, orthostatic hypotension falls, coat hanger pain, sexual dysfunction, hyper sexuality, erectile impotence, dry eyes</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>Dribbling of saliva, dysphagia, reflux, constipation, unsatisfactory voiding of bowel, faecal incontinence</td>
</tr>
<tr>
<td>Sensory symptoms</td>
<td>Pain, paraesthesia, olfactory disturbance, visual disturbance</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>Fatigue, hiccups, seborrhoea</td>
</tr>
</tbody>
</table>

Though NMS of PD occurs mainly in advanced stages of PD, some studies have shown that in up to 21% of PD patients these symptoms may predate the motor symptoms by more than a decade\(^3\). Symptoms more likely to precede the motor symptoms are olfactory problems; depression, constipation and rapid-eye movement (REM) sleep behaviour disorder (RBD). Such a presentation can lead to inappropriate referrals and hence delayed diagnosis and treatment\(^4\).

The burden of the spontaneous or de novo NMS of PD can be exacerbated by the frequently induced iatrogenic NMS as side effects of anti Parkinsonian treatment these include postural hypotension, hallucinations and sleep problems.

**Pathophysiology of NMS**

Although understanding of the neuroanatomical and neurochemical changes in PD continued to improve, the exact pathophysiology of NMS in PD remains speculative. The old perception that neurodegeneration of dopaminergic cells in the SN herald the pathological process in PD has been challenged by Braak and colleagues\(^5\). Indeed, the motor symptoms of PD are overt when there is considerable loss of dopaminergic neurons in SN pars compacta. However, NMS predating the motor features of PD reflect the progression of lewy pathology in PD\(^5\).

A six-stage pathological process concept has been suggested by Braak and colleagues\(^5\) as follows:

**Braak stage 1**
The degeneration of the olfactory bulb and the anterior olfactory nucleus, clinically resulting as problems in the sense of smell.

**Braak stage 2**
The progression of the Lewy pathology to lower brain stem; these areas are involved in the sleep - awake cycles and autonomic functions. In this area, some brain stem nuclei such as raphe nucleus (serotonin), locus coeruleus (norepinephrine) and the pedunculopontine nucleus are involved and thought to be major causes in REM sleep behavioural disorder (RBD) and visual hallucinations.

Medullary nuclei are also important in controlling autonomic functions\(^6\).

**Braak stages 3 and 4**
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structures. In these stages patients may manifest neuropsychiatric symptoms such as anxiety, depression, cognitive problems and visual hallucinations.

Axons from the main dopaminergic areas in the basal ganglia (BG) project in an organised pattern forming sensorimotor, associative and limbic pathways with inputs in the subthalamic nucleus, the main target from deep brain surgery in PD\(^7\).

The palladium-subthalamic nucleus is regarded as the anatomical base for most of the NM functions of the BG\(^8\).

**Spectrum of NMS in PD**

**Sleep problems**

Sleep problems are amongst the most frequent NMS in PD\(^9\) and usually start early in the disease course\(^10\). They can be primary due to PD itself, but could also be exacerbated or secondary to a range of problems associated with PD. The primary sleep problems are, in general, a result of the degenerative pathological and chemical changes in the central sleep regulations centres in the brain stem and thalamocortical pathways. Dopamine and other neurotransmitters may also be important in the sleep problem in PD.

Clinical evidence suggests that somnolence can be induced by some dopamine agonists particularly at lower doses, whereas wakefulness is induced at higher doses\(^11\). Dopamine also shares some structural similarities with some wake-promoting drugs. Major dopaminergic areas such as the ventral tegmental areas receive hypothalamic peptides implicated in wakefulness.

**REM sleep behaviour disorder (RBD)**

A form of parasomnia, occurring in about a third of PD patients\(^12\), during which there is lack of the muscle atonia expected at this age. This enables patients to perform complex movements to physically enact their dreams which can be vivid, frightening or unpleasant. Partners can report talking, shouting, verbal threats, violent assaults and falling out of bed during sleep. REM behaviour disorders can precede the motor symptoms in up to 40% of PD patients\(^12\). The exact pathway remains speculative, but seems to be more associated with degeneration of the lower brain stem nuclei.

Imaging studies of isolated cases of REM sleep behaviour disorder has confirmed symmetrical small reductions of dopaminergic uptake.

Some drugs that showed beneficial effect in treatment of RBD include pramipexole\(^13\), levodopa\(^14\), gabapentin and melatonin. However clonazepam is probably the most effective treatment of this disorder in PD patients\(^15\).

**Insomnia**

Either sleep onset insomnia, i.e. difficulty initiating sleep, or sleep maintenance insomnia with frequent awakenings.

Factors contributing to insomnia include:

- Restless leg syndrome RLS
- Periodic limb movement in sleep
- Nocturnal akinesia
- Off-period dystoma
- Nocturnal tremors
- Pain
- Nocturia:
  - Detrusor overactivity
  - Diuretics
  - Prostatic disease
  - GORD
  - Heart failure

**Excessive daytime sleepiness (EDS)**

Excessive day time sleepiness (EDS) can occur in up to 50% of PD patients and may precede the typical motor symptoms\(^16\). EDS is multifactorial likely resulting from the disturbance of the nocturnal sleep, the pathological changes in PD, and to the drug treatment.

Physicians dealing with PD patients should ask patients about EDS due to its impact on patients’ quality of life and its dangers for those who drive.
Neuropsychiatric problems

Depression
Depression is an important neuropsychiatric symptom in PD occurring in up to 45% of patients. Damage to serotonergic, dopaminergic and norepinephrine projections in the limbic system is implicated.

Depressed patients with PD have a low concentration of 5-hydroxy indoleacetic acid, a serotonin metabolite, in the cerebrospinal fluid and reduced cortical 5-HT1A receptor binding compared to non-depressed PD patients.

Symptoms of depression in PD include loss of interest and initiative, fatigue, indecisiveness, panic attacks, feeling of guilt and apathy. Although suicidal ideation is relatively common in PD, death by suicide is rare, with exception of patients undergoing subthalamic nucleus stimulation.

Symptoms of depression can precede the development of PD.

Pramipexole, a dopamine agonist, used in the treatment of the motor symptoms of PD had shown antidepressant activity similar to or even better than fluoxetine and sertraline. Prolonged release ropinirole has also shown positive effect in the mood of PD patients.

In the case of the two dopamine agonists, motor improvement could be contributing to the improvement in the depressive symptoms.

Anxiety
Anxiety is common in PD and usually coexists with depression and can predate the motor symptoms. It can be present as a generalised anxiety disorder, panic attack, or social phobias. It is clinically more noticeable during the “wearing off” periods manifesting itself as panic attacks. Therefore, it can respond to dopaminergic medications targeting the wearing off. However, anxiety can persists independent of the dopaminergic state. Some studies suggest that depression and anxiety are more common with left sided motor symptoms.

Deep brain stimulation of the subthalamic nucleus has shown superiority in improving anxiety compared to conventional medical treatment.

Apathy
Apathy is an established symptom of PD independent of depression or anxiety, although it may coexist with both. Patients equally disabled as a result of diseases other than PD don’t show the same level of apathy compared to PD patients with the same disability, indicating neurodegenerative contribution.

Other negative symptoms such as anhedonia and fatigue can also be due to degenerative changes in reward centres such as dopaminergic projections between the ventral tegmentum and nucleus accumbens or areas that mediate goal-directed behaviour, e.g. frontal subcortical areas.

Apathy responds only partially to dopaminergic drugs indicating the involvement of other neurotransmitters. Testosterone deficiency is also thought to play a role in the occurrence of these negative symptoms.

Cognitive impairment
Subtle cognitive deficits are almost universally identified in PD patients even at early stages. However, frank dementia can occur in up to 40% of people with PD. Dementia is progressive and can manifest as frontal executive dysfunction with impaired problem-solving, organization and planning, and impairment of visuospatial abilities. It is associated with rapid progression of the disease with significant impact on the patients’ independence, resulting in increasing nursing home placements, and mortality. The underlying pathology includes degeneration of nigral and cholinergic cells and the presence of cortical and subcortical Lewy bodies. Other pathologies contributing to dementia in PD include Alzheimer’s disease, vascular pathology and possible genetic association with APOE genotype.
Volumetric MRI studies of PD patients with dementia have shown hippocampal volume reduction to a similar extent to that in Alzheimer’s disease\(^\text{37}\). The clinical profile of PD dementia includes features of frontal dysexecutive syndrome as well as hallucination, psychosis, mood and personality disorders while language and praxis remain largely intact\(^\text{38}\). Anticholinesterases have shown improvement in cognitive function and psychotic behaviour in PD dementia\(^\text{38}\).

**Psychosis and visual hallucinations**

The prevalence of hallucination in PD is high occurring in up to 40% of patients\(^\text{39}\) and with psychosis constitutes a major risk factor for Nursing Home placement\(^\text{34}\). Hallucinations usually start as benign visual illusions but progress into more sinister symptoms of psychosis such as delusions, paranoid ideation and delirium. Auditory and tactile hallucinations are less common and when present usually occur in association with visual hallucinations\(^\text{40}\).

Risk factors for hallucinations include RBD, cognitive impairment and genetic predisposition. Degeneration of the pedunculopontine nucleus, locus coeruleus and the dopaminergic raphe nuclei, all implicated in the causation of RBD, may be causative\(^\text{41}\). Hallucination, although benign at the start, can turn into nasty paranoid accusatory delusion distressing to both carers and relatives. Treatment of psychotic symptoms includes atypical antipsychotics (quetiapine and clozapine) and cholinesterase inhibitors.

**Dysautonomia**

Pathology of autonomic dysfunction in PD is complex and includes degeneration of nuclei mediating autonomic functions, such as the dorsal vagal nucleus, nucleus ambiguous and other medullary centres\(^\text{46}\).

Unlike multisystem atrophy dysautonomia is a late manifestation in PD with possible exception of early cardiac sympathetic denervation in PD and not multisystem atrophy\(^\text{42}\).

Clinically autonomic dysfunction in PD can be present with symptoms related to postural hypotension, bladder dysfunction, erectile dysfunction, constipation and hyperhidrosis. Autonomic function in PD can objectively be assessed by several tests such as QSART (quantitative sudomotor axon reflex test for sudomotor function), urodynamic studies, defecating proctography, tilt table test and pupil function test.

**Bladder dysfunction**

Urinary urgency is common in PD resulting from detrusor overactivity. This is thought to be due to a combination of underactive D1 receptor with possible over stimulated D2 receptor in the bladder. PD patients might also experience obstructive symptoms with voiding difficulties due to disorder of bladder contractility or abnormal sphincter action but seems to be reversible on apomorphine\(^\text{43}\). Symptoms of voiding difficulties seems also to improve during the “on” phase with levodopa although urinary urgency is unchanged or worsened\(^\text{44}\). Deep brain stimulation of the subthalamic nucleus has a positive effect on bladder function by improving bladder capacity\(^\text{45}\). Nocturia is common in PD and may occur due to a combination of decreased bladder capacity, increased urine output at night and sleep impairment.

**Sexual dysfunction**

Sexual dysfunction is common in PD and can be part of the spectrum of dysautonomia. Presentation includes erectile dysfunction, decreased libido and hyper sexuality\(^\text{46}\). Testosterone deficiency is thought to be implicated\(^\text{31}\). Apparent sexual behaviour and hyper sexuality is a recognized side-effect of dopaminergic drugs and apomorphine has been reported to cause penile erection in PD patients\(^\text{47}\).

**Gastro intestinal symptoms**

Constipation is common in PD occurring in up
to 60% of patients\textsuperscript{(48)}. Although studies suggest loss of both central and colonic dopaminergic neurones, constipation poorly responds to dopaminergic treatment suggesting the implication of other mechanisms\textsuperscript{(49)}. Similar to olfactory problems, constipation may predate the motor features of PD.

**Practical management of autonomic dysfunction in PD:**

- **Postural hypotension**
  - High salt intake
  - Elastic stockings
  - Adequate fluid intake
  - Head up tilt
  - Fluchocortisone 100 to 300µg daily
  - Midodrine 2.5 to 10mg daily
- **Bladder dysfunction**
  - Detrusor hyperreflexia: anticholinergics, oxybutynin, tolterodine, trospium chloride
  - Retention: betahanechol chloride 25 to 75mg a day, intermittent Self Catheterization
  - Nocturnal polyuria: desmopressin spray 10 to 40µg a night
- **Erectile dysfunction**
  - Sildenafil
  - Sublingual Apomorphine
- **Constipation**
  - Stop anticholinergics
  - Adequate fluid intake
  - Rule out other causes (hypothyroidism, hypercalcaemia, low potassium)
  - Laxatives

**Olfactory dysfunction**

Thought to be due to degeneration of the olfactory bulb and the anterior olfactory nucleus, is a potential preclinical maker of PD. Hyposmia has also been reported in asymptomatic relatives of PD patients, some of whom, developed clinical manifestation of the disease, while others had presynaptic abnormalities detected on SPECT following a period of follow-ups\textsuperscript{(50)}.

**Pain in PD**

Unexplained pain is common in PD and constitutes a major component of the NMS. It has been reported in as many as 29% of PD patients\textsuperscript{(51)} i.e.

- Central pain is an endogenous pain associated with hyperalgesia and reduced threshold for heat pain. This pain is thought to be secondary to impairment of autonomic functions.
- Burning mouth is present as a continuous burning sensation of the oral mucosa and tongue. Contributory factors may be vitamins and mineral deficiencies, xerostomia, candidal infections and malfunctioning dentures. It could also be associated with levodopa\textsuperscript{(52)}.
- Visceral pain can be due to constipation or the rare development of retroperitoneal fibrosis related to the use of some ergot dopamine agonist.

**Types of pain in PD:**

- **Musculoskeletal pain**
  - Rigidity
  - Dyskinesia
  - Dystonia
  - Off period generalised pain
- **Nocturnal pain**
  - Restless leg syndrome
- **Postural hypotension pain**
  - Pain around the shoulder area and neck
- **Orofacial pain**
  - Tempromandibular joint pain
  - Burning mouth syndrome
- **Visceral pain**
  - Constipation
  - Retroperitoneal fibrosis
- **Primary central pain**

**Visual function in PD**

Colour and contrast discrimination has been noticed and could even be a premotor marker for PD\textsuperscript{(53,54)}. Retinal dysfunction in PD has been confirmed on Electoretinography and thought to be the result of reduced retinal dopamine concentration\textsuperscript{(55,56)}.
In conclusion, the NMS in PD are complex and involve multi system dysfunctions, sensory, autonomic, and neuropsychiatric. Though significantly has impact on a patient’s quality of life they still remain frequently overlooked. There is increasing evidence that non motor symptoms antedate the clinical motor manifestations by years or even decades and thus may turn out to be critical clues in early diagnosis and identification of at-risk populations. Quantitative and validated scales for assessment of non-motor symptoms are essential to improve early detection of these symptoms.

References
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