Spectrum of Non-Motor Symptoms in Parkinson's Disease — a Review

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Abstract

Motor and non-motor symptoms of Parkinson's disease (PD) and their management have been evaluated in numerous studies. Four classical symptoms, including bradykinesia, tremor, rigidity, and postural abnormalities, are used to establish a clinical diagnosis of PD. However, this research is aimed at exploring the range of non-motor symptoms with an emphasis upon their ability to affect the patients with PD and their quality of life.

With a slow onset of the known symptoms like tremor or rhythmic shaking of limbs called "pill-rolling tremor", slowed movement (bradykinesia), muscle rigidity, stooped and altered posture, loss of the ability to blink or smile, and various speech and writing changes; the disease takes a leap into the non-motor symptoms like dementia, drooling, swallowing issues, difficulty urinating, and constipation. The dopaminergic pathophysiology of PD explains the anxiety, slowness of thought, fatigue, and dysphoria. Knowing the non-motor symptoms is crucial to help the clinician to make early diagnosis and to better understand the prognosis of the spectrum of this disease.

Keywords: *Parkinson's disease; non-motor symptoms; dementia; cognitive impairment; sleep disorders*

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Немоторные симптомы болезни Паркинсона: обзор

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Аннотация

Моторным и немоторным симптомам болезни Паркинсона (БП) и их лечению посвящён целый ряд исследований. Клинический диагноз «болезнь Паркинсона» устанавливается по наличию четырёх классических симптомов: брадикинезии, тремора, ригидности мышц и постуральных нарушений. Цель настоящего исследования состоит в изучении спектра немоторных симптомов и их влияния на качество жизни пациентов с БП.

В то время как такие симптомы болезни, как тремор по типу «скатывания пилюль», замедленность движений (брадикинезия), ригидность мышц, сутулость и постуральные нарушения, нарушение способности моргать или улыбаться, а также различные изменения речи и письма, развиваются медленно, на более ранних стадиях БП возникают немоторные симптомы: деменция, слюнотечение, нарушения глотания, затруднённое мочеиспускание и запор. Патофизиологические процессы, связанные с дофаминергической системой, обусловливают возникновение тревоги, замедление мышления, утомляемость и дисфорию у пациентов с БП. Знание немоторных симптомов необходимо для постановки диагноза на ранней стадии и улучшения прогноза для нарушений этого спектра.

Ключевые слова: *болезнь Паркинсона; немоторные симптомы; деменция; когнитивные нарушения; нарушения сна*

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Introduction

Dr. James Parkinson defined Parkinson's disease (PD) as a chronic neurodegenerative disorder of the extrapyramidal system. The disease is characterized by both motor and non-motor symptoms. The motor symptoms like bradykinesia, pill-rolling tremors, rigidity, etc. develop due to the degeneration of dopaminergic neurons in nigrostriatal pathway [1]. A progressive degeneration of dopaminergic neurons occurs in the pars compacta region of substantia nigra which projects to the striatum via the nigrostriatal pathway leading to a decline of dopaminergic functions in the patients. Most patients are reported to develop PD when there is 50% to 80% loss of dopaminergic neurons. The increased activity in globus pallidus internus segment and substantia nigra pars reticulata circuit is observed when there are decreased levels of dopamine in the striatum of PD patients, which contributes to abnormal functioning of gamma aminobutyric acid, resulting in inhibition of thalamus and reduced ability of thalamus to stimulate frontal cortex, leading to the reduced motor activity that is a feature of PD [1]. With no conclusive tests to confirm the diagnosis of PD, clinicians must rule out other diagnoses by assessing the history and symptoms.

The classical triad includes bradykinesia, rigidity and tremor at rest. Dysarthria, postural instability, and dystonia are other motor features of PD. Besides, further diagnostic workup including neuropsychiatric testing, sleep analysis, and assessment of vision should be carried out in suspected PD cases. Abnormal colour vision is, for instance, a non-motor symptom occurring due to the changes in intraretinal dopaminergic transmission. Thus, it becomes very important to be aware of the non-motor symptoms and consider them during clinical diagnosis [1].

The disease is generally managed by oral levodopa. With rehabilitation and physiotherapy as established therapeutic options to manage symptoms of PD, there are other new rehabilitation modalities used nowadays. In light of the necessity to underscore the significance of non-motor symptoms in patients with PD, this review has been prepared. It addresses various questions around the unchartered territory of non-motor manifestations and the approaches to their management.

Non-motor symptoms of Parkinson's disease

Depression

As described above, treatment of PD is complex. Besides movement disorders, it revolves around diminishing the behavioural abnormalities. The patients are prone to psychiatric conditions seen in the rest of the population like depression and cognitive impairment. As per B. Scott et al., out of a sample of 948 patients, about 36% presented with depression [2]. A meta-analysis pointed out that about one third of patients have clinically significant depression [3]. Another review mentions that around 50% of PD patients are affected by depression that may take a progressive course, with the development of anxiety and panic attacks [4]. Depression and anxiety may occur long before diagnosis is even made [5]. In a 2008 review article, it was implied that depression is common in patients with PD and it was found in 35% of PD patients [6]. However, depression is milder in patients with PD in contrast to those unaffected with PD; the PD patients with depression also present with apathy and anhedonia. Moreover, depression is seen early before the onset of motor symptoms and is linked to the duration and severity of motor symptoms. It also depends on the fluctuations of these symptoms and the dosage variations of dopaminergic medications. Factors like psychosis, sleep disturbances, anxiety and so on can lead to an increased risk of developing depression in PD. Loss of cortical cholinergic neurons may cause depression in patients with PD [7].

Anxiety

60% of patients with PD are affected by anxiety, which in general includes fear, worry, and apprehension and may not always be accompanied by depression [7]. It is more frequent in females and patients with very early disease onset. Associated with periods of low dopamine levels, anxiety levels proportionally increase with motor fluctuations and freezing (no movements) [8]. In a study conducted with 105 PD patients PD, anxiety was prospectively assessed based on the Parkinson Anxiety Scale, and Parkinson's Disease Questionnaire. Results showed that 56 patients had anxiety: episodic anxiety (50%) and persistent anxiety (15%). Higher prevalence of episodic anxiety is a PD-specific symptom and stems from the dopaminergic pathway [9]. Such anxiety episodes are often

related to verbal memory loss in PD patients with no symptoms of dementia. As such, the anxiety exerts an adverse influence on the quality of life and proper timely screening is a must to ensure the efficient delivery of care and management to PD patients and their close ones [9].

Cognitive impairment and dementia

Cognitive impairment and dementia may complicate PD. I. Galtier et al. conducted a study which included 43 patients with idiopathic PD and 20 neurologically normal controls who were followed up for the MDS (Movement disorder society) Task Force criteria for PD-MCI (mild cognitive impairment) diagnosis [10]. 96.2% was the maximum frequency for the multiple domain impairment and around 42.3% of PD-MCI patients had dementia when followed up. The logistic regression had clearly shown that the Hoehn–Yahr stage and education significantly contributed to the prediction of PD-MCI while Hoehn–Yahr stage and memory domain predicted dementia. Neurological deterioration, level of education, and loss of memory were prognostic factors for the progression of intellectual impairment [10]. The general trend which is seen in PD patient is an impairment of the executive dysfunctions) and visuospatial function, with less prominent memory deficits and preserved language function. Unstable set shifting, attention and planning comprising the executive dysfunction are seen early in the course of the disease, and this may even include impaired face recognition. Other measures of visuospatial functions degrade over the progress and severity of PD and dementia. Finally, the brain higher level functions get abnormal even before the patients gets diagnosed with dementia [10].

The percentage of dementia in population due to PD is 3–4%. Cross-sectional studies have shown that the mean prevalence of dementia is 40%. In prospective cohort studies, the incidence rates of dementia in patients with PD approximate 100 per 1000 patient-years which is five to six times higher than in controls without PD [11]. Memory deficits are not too rare in PD dementia but are adjoined to retrieval of information that is learned and known. Aphasia, apraxia, and severe memory loss are mostly seen in Alzheimer disease. Neuropsychiatric symptoms may occur in PD without dementia; however, they are increasingly more common in patients with more drastic cognitive impairment [12].

Hallucinations

Visual hallucinations affect up to 75% of PD patients. It not only impacts patient's life but also affects their family. One of the common hallucinations type is visual hallucinations. They were shown to be the strongest predictor of earlier placement in care homes, cognitive decline, and increased mortality. They occur mostly in the evening and involve perception of animals, people etc. [13]. The affected person experiences minor hallucinations and misinterprets objects, such as pile of clothes, dogs and cats and hears muffled and distorted sounds (auditory hallucinations). Some patients experience tactile, gustatory, or olfactory hallucinations. They feel the presence of someone and illusion of objects passing across the peripheral vision [14]. The prevalence estimate of visual hallucinations is 8.8% to 44%. The feeling of a presence of odd things, complex frightening visions, and some vague feelings is the entire visual phenomena span in visual hallucinations. Underreporting is a potential problem since patients fear of being labelled as "mad" [15].

Generally, it occurs to the patient in dim surroundings when they are alert and usually the eyes are open. It has been reported that a blurry image appears suddenly around the visual field without any voluntary effort. This episode persists for few seconds and vanishes out suddenly. These hallucinations were complex and contained inanimate objects or persons, but they were transient and perceptual. Usually there are five or less images, sometimes being meaningful to the patient, happening in dim areas, recurrent and non-threatening. How much the patient remembers of these hallucinations can change over time and depends on the cognitive impairment.

21.5% of the participants out of a total of 191 patients without dementia who were administered the Parkinson Psychosis Rating Scale had psychosis. In this sample, 13.6% had visual hallucinations, 6.8% of these had auditory hallucinations, 7.3% presented with illusions and 4.7% with paranoid ideation. Auditory hallucinations were also found in PD patients even though they were less common than visual hallucinations [16]. In a study with 121 PD patients, 8% had auditory hallucinations. The reports also show occurrence of erotomania, jealousy, and persecutory delusions. Unique entities such as Cotard Syndrome and Capgras syndrome have been also seen in PD patients [16].

Constipation

A non-motor symptom of constipation can occur early before the motor symptoms. The gastrointestinal symptoms are very common during all stages of PD, with 30% patients reporting drooling, dysphagia, gastroparesis, and constipation [17]. The reported constipation prevalence is 8% to 70% and is steadily rising as the disease progresses [17, 18]. The median prevalence of 44% was noted if the criterion of less than three bowel movements per week or straining is considered. The data points out that as compared to the general population the prevalence of constipation raises by a median of 30 percentage points in PD patients.

The difficult rectal evacuation seen in PD patients is not because of rectal hyposensitivity, and rather it is caused by the abnormal tone of the striated external sphincter and puborectalis muscles [19]. In cross-sectional studies, small intestine bacterial overgrowth is more often seen in patients with PD compared to healthy controls with a prevalence of 25% to 54% [20].

Gastrointestinal dysfunction with drooling

In the study conducted in PD patients in Charles Nicolle Hospital of Tunis during 2013 to 2014, 73% subjects had gastrointestinal symptoms as most common non-motor symptoms diagnosed with endoscopy and immunohistochemical study; these symptoms can be looked upon as a marker of PD [21]. The incidence of dysphagia ranges from 9% to 82% but has been noted up to 97% in objective studies [22]. In advanced PD patients who have severe bradykinesia and rigidity it leads to the oropharyngeal dysphagia. The incidence of gastroparesis is somewhere between 70% to 100% in mild PD patients with a mean half emptying time of 46 to 149 minutes and 55 to 221 minutes in moderate PD compared to 43 to 107 minutes in healthy controls. The distal oesophageal transit times and colonic transit times were both extended in early to moderate PD [20].

A non-motor symptom that affects more than half of patients with PD, excessive salivation, has a negative impact on their lives, especially in advanced stages. Along with drooling, the patients also presented with the lower swallowing capability, poorer functional swallowing, more severe facial hypokinesia and severe involuntary mouth opening. The incidence of drooling in PD ranges from 10% to 84% [21, 22]. The droolers showed more stooped posture. The presentation relates to abnormal swallowing in the oropharyngeal phase and an increased frequency of secretions of the parotid gland.

Till now, the pathophysiology of drooling in PD is not fully understood with reduced intra-oral salivary clearance expected to be the major cause of it [21]. Of all factors contributing to drooling, hypomimia was most strongly linked to and more seen in men with advanced PD and dysphagia [22]. Dysphagia is considered an important component in the multifactorial model which explained drooling. In fact, latest findings seem to prove that tongue bradykinesia is related to both oropharyngeal dysphagia and drooling [22].

In a study conducted in 84 patients at Mayo Clinic, ten showed delayed gastric emptying, another ten had slow colonic transit, sixteen had accelerated gastric emptying and 49 had normal transit time [23].

Dysphagia

Dysphagia was reported to affect 68% of late-stage PD patients (Hoehn–Yahr stages 4 and 5) in Barcelona and Lisbon cohort. A relevant unexplained weight loss or BMI (body mass index) below 20 suggests dysphagia [24]. During the course of disease around 20% of PD patients develop malnutrition. Sialorrhea or drooling is a predictor of dysphagia and aspiration pneumonia [24].

Rhinorrhoea

Rhinorrhoea refers to the presence of nasal discharge which is the “presence of nasal drainage in the absence of sinus problems, respiratory infections, and allergies”. In a systematic review for determination of rhinorrhoea incidence in PD in 451 patients and 233 controls, pooled prevalence of the symptom was 45%, and a greater number of patients with rhinorrhoea self-reported disturbances in smell compared to those without abnormal nasal disharge. The mean age of patients with PD and rhinorrhoea was significantly greater than those with PD without rhinorrhoea. No difference in disease duration, disease severity, or gender between the cohorts was identified [25].

Hyposmia

More than 90% of PD patients develop hyposmia or anosmia which is generally bilateral and occurs before motor symptoms due to dopamine deficiency. Patients generally do not report it but if the development or progression of hyposmia is associated with other early clinical, imaging and/or biochemical markers it could be viewed as a biomarker for detection of early pre-motor PD [26].

Othello syndrome

Of 805 patients with PD, 20 had delusional jealousy, which was associated with treatment with a dopamine agonist, and in five patients it can be treated by reducing the dose of dopamine agonist [27]. The patient can exhibit delusional jealousy in the evening or midnight or while indoors, but it can also sometimes happen during daytime or while outdoors. In the study review, the DSM-IV-TR (The Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision) criteria were used. Unlike visual hallucinations, patients did not see persons or animals and were fully oriented. There was no abnormal odd or repetitive behaviour. These patients did not have any premorbid personality disorder prior to Othello syndrome, or any family history of psychiatric or personality disorders [28].

There are limited studies of Othello syndrome in PD and one such study identified eleven Othello syndrome subjects (nine males; two females) out of 153 patients who were found to have PD as per the Movement Disorders Society Criteria [29]. It was noted that Othello syndrome is more frequently seen in males; however, the incidence of this syndrome is 7.2% only [28].

Sexual dysfunction

Often neglected non-motor symptom, sexual dysfunction (SD) in PD patients is attributable to numerous social and cultural factors which is why it is still under-recognised. PD affects libido and there is orgasmic dysfunction in men

and women [30]. A multidisciplinary approach for diagnosis and treatment must be undertaken to assess the plethora of symptoms of SD in PD. More so, prevalence of SD in women is approximated around 25% to 63% with a greater prevalence in post-menopausal women [31]. Diminished libido and erectile dysfunction can occur in 80% of male PD patients and orgasmic dysfunction may reach up to 84% and 75% in female PD patients [32]. In 15% of cases symptoms appear early in PD developing over 65 years of age [33]. But even the young PD patients get affected by the symptoms of SD. They show decreased sexual desire and are feel discontented with sexual life.

Male sexual dysfunction is relatively more prevalent, and men have difficulties reaching orgasm and experience premature ejaculation. Women show predominant decrease in sexual desire and difficulties with arousal and orgasm. Decreased libido along with vaginal tightness, involuntary urination, and displeasure in sexual intercourse is also observed in females with PD [32].

Sleep disturbances

Sleep disturbances are one of the major non-motor symptoms in PD, including rapid eye movement (REM) sleep behaviour disorder (RBD), restless leg syndrome, and sleep apnoea. High percentages of people with sleep disorders are expected to develop PD, even though RBD is found to be in the best association with PD development. The probable risk is substantially greater for acquiring PD in patients with RBD compared to the general population, and once PD is initiated, the progression of motor symptoms is quicker than in patients with no RBD [5].

Urinary symptoms

Urinary frequency and retention is generally seen in patients with PD. This occurs due to disturbances in cholinergic parasympathetic nervous system. It has been noted that nigrostriatal degeneration might be responsible for urinary symptoms. Frequent nocturia is seen in 60% of patients and is caused by detrusor overactivity [34].

Conclusion

This review discusses all the non-motor symptoms of PD. The aim of this review was to present major non-motor symptoms that affect PD patients. Knowing the non-motor symptoms is crucial to help the clinician to make early diagnosis and for better prognosis of disease. These non-motor symptoms are treated specifically (Table) to ensure better relief and improve the quality of patients' life. Hyposmia, is a biomarker for the early pre-motor PD, and when combined with imaging and non-motor tests for diagnosis, it can help identify PD early.

Treatment aspects related to non-motor symptoms of Parkinson's disease

Non-motor symptoms	Treatment
Depression	• Use of antidepressants: selective serotonin reuptake inhibitors remain the drug of choice [35]; • cognitive behavioural therapy; • monoamine oxidase type B inhibitors, tricyclic antidepressants, and dopamine agonists can also be used to treat depression [36–40]
Anxiety	Clonazepam, benzodiazepines, and selective serotonin reuptake inhibitors [41–43]
Cognitive impairment and dementia	• Non-pharmacological approaches: — cognitive interventions, non-invasive brain stimulation, physical exercise [44]; • rivastigmine is approved for PD: available as capsules and transdermal patch [45]; • donepezil improves cognitive performance
Hallucinations	Hallucinations can be treated with clozapine in PD patients [46]
Constipation	• Macrogol; • lubiprostone; • cisapride; • mosapride; • tegaserod; • relamorelin [47]
Gastrointestinal dysfunction and drooling	• Catechol-O-methyl transferase inhibitors, monoamine oxidase type B inhibitors and amantadine are used to treat gastrointestinal dysfunction in PD patients [45]; • domperidone, 10 mg; • mosapride, 15 mg with dose titration from 10–15 mg/week to 45 mg; • non-pharmacological options: regular physical activity for overall benefit to the PD patients [48]
Rhinorrhea	• Antihistamines; • anticholinergic sprays; • topical steroid nasal sprays; • vidian neurectomy, cryotherapy; • radiofrequency ablation [25]
Dysphagia	• Dysphagia can be decreased by asking PD patients to do swallow manoeuvres [49]; • dietary modifications can also help to reduce dysphagia; • oral motor exercises [50]
Hyposmia	Deep brain stimulation can reduce hyposmia [51]
Othello syndrome	Discontinuing or reducing dose of dopamine agonists in PD patients with Othello Syndrome plus aripiprazole and quetiapine [52]
Sexual dysfunction	• Newly diagnosed PD patient — first start with dopaminergic drugs and ensure a follow up; • use of antidepressants like clomipramine; selective serotonin reuptake inhibitors such as sertraline may be successful; • sildenafil is an effective treatment option along with tadalafil and vardenafil; • sublingual apomorphine; • prostaglandin E1, papaverine and papaverine-phentolamine mixture are also effective [53]
Sleep disturbances	• Levodopa/carbidopa-controlled release (CR), eszopiclone, melatonin 3 to 5 mg can be used for the treatment of insomnia and modafinil for the treatment of excessive daytime sleepiness [54]
Urinary disturbances	Anticholinergics are used for urinary retention. Diazepam, baclofen or dantrolene may be useful in relaxing striated muscle in patients with hyper-reflexic external sphincters. Serotonergic agents such as duloxetine may be used to treat overactive bladder in PD [34]

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