



## THE NON-MOTOR SYMPTOMS–CHALLENGE IN DIAGNOSIS OF PARKINSON'S DISEASE

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### ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disorder after the dementia of Alzheimer. The clinical presentation of PD is dominated by typical motor symptoms as resting tremor, cogwheel rigidity, bradykinesia, and postural instability. Non-motor symptoms (NMS) of Parkinson's disease are common but are often under-recognized in clinical practice either due to the lack of spontaneous complaints by the patients or to the absence of systematic questioning by healthcare professionals. In contrast to motor dysfunctions, non-motor symptoms frequently remain unreported. Recently, a self-completed NMS questionnaire and NMS scale for identification and evaluation of these symptoms have been validated. An international survey has shown that up to 62% of NMS in PD remain undeclared to healthcare professionals because patients are unaware that NMS symptoms are linked to PD. Based on both clinical and neuropathological data, PD, traditionally accepted as a dopaminergic motor disorder, now can be characterized as a multisystem neurodegenerative disease that involves many neurotransmitter systems and affects not only motor but non-motor functions, too.

**Keywords:** Parkinson's disease (PD), Non-motor symptoms (NMS), quality of life,

### INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer dementia. The clinical presentation of PD is represented mainly by resting tremor, cogwheel rigidity, bradykinesia, and postural instability [1]. Although the exact cause of the disease remains unknown, many investigators believe that it results from an interaction between genetic and environmental factors that lead to progressive degeneration of neurons in susceptible regions of the brain. Despite decades of hard investigations, the identification of most of these factors, the nature of their interactions, and the molecular pathways of neurodegeneration initiated by them, are still poorly understood. [2].

### EPIDEMIOLOGY

PD may start early–in the 3rd decade (onset before the age of 40 is defined as young-onset PD), but it usually starts later. About 1–2 persons per 1000 of the popu-

lation suffer from PD. The prevalence of PD tends to increase with ageing, and approximately 1% of the population above 60 years is affected by PD [3]. According to the epidemiological study of Van Den Eeden SK et al., the incidence of PD rapidly increases over the age of 60 years, with only 4% of the cases being under the age of 50 years.[4]. In Bulgaria, no official data concerning the incidence of PD have been published. Taking into consideration that the population of Bulgaria is about 7.500.000, the indicative number of patients with PD must be about 12.000-13.000 [5].

### NON – MOTOR SYMPTOMS OF PD (NMSPD)

Non–motor symptoms (NMS) of Parkinson's disease (PD) are common, but are often underrecognized in clinical practice because of the lack of spontaneous complaints by the patients, or by the absence of systematic questioning from the healthcare professionals [6]. In contrast to the evident motor dysfunctions, the non–motor symptoms, frequently remain unreported and hidden for the examiner. Recently, a self-completed NMS questionnaire and NMS scale for identification and evaluation of NMS in PD have been validated. An international survey has shown that up to 62% of NMS in PD may remain undeclared to healthcare professionals because patients may be unaware that the symptoms are linked to PD [7]. NMSs in PD were systematically described for the first time in 2006 by Chaudhuri et al. [7]. They are found in a large proportion of patients with PD, and consist of autonomic dysfunctions, sensory complaints, neuropsychiatric disturbances, sleep disorders, fatigue, and others [8]. The most common NMS are usually described and grouped in clusters according to their pathogenesis as follows [6]: (A) Neuropsychiatric symptoms; (B) Sleep disorders; (C) Fatigue; (D) Sensory symptoms; (E) Autonomic dysfunctions.

### DESCRIPTION OF NMS

#### A. Neuropsychiatric symptoms

**Depression.** The clinical presentation of depression in PD is specific. In PD patients, somatic features as lack of energy and psychomotor slowing, irritability, but no guilty or failing feeling are found predominantly present. Depression is associated with sleep disorders, lack of refreshing sleep, a decrease of libido, and feeling of poor physical appearance [6].

**Apathy.** Apathy is characterized by loss of motivation, affecting mainly emotional and intellectual domains, and the behavior also. It is defined as one of the major determinants of reduced quality of life in PD[6].

**Anxiety.** Generalized anxiety (with a feeling of situational security) appears to be frequent in PD, as well as, single phobia, social phobia, and panic trouble. Anxiety is twice more frequent in PD compared with the general population [10]. Prevalence rates of depressive disorders in PD vary widely across studies, ranging from 2.7% to more than 90% because of inconsistent methods and case diagnoses [10]. Anxiety often accompanies depression in up to 40% of patients with PD[11].

**Impulse control disorders (ICDs).** ICDs are behavioral disorders characterized by failure to resist an impulse, inability to cut down and unsuccessful attempts to control a specific behavior. ICDs include pathological gambling, hypersexuality, compulsive shopping, and binge or compulsive eating. [6]. ICDs occur in 15% to 20% of PD patients, and their prevalence has been found increased among patients treated with dopamine agonists, compared with patients not taking dopamine agonists [12].

**Dopamine Dysregulation Syndrome (DDS).** Also named hedonistic homeostatic dysregulation in PD, DDS has been recently defined as compulsive use of dopaminergic drugs, associated with severe behavioral symptoms, and impaired social functioning. DDS consists of a craving or intense desire to obtain the medication, even in the absence of motor symptoms [13].

**Hallucinations, delusions, illusions.** Visual hallucinations/illusions are most commonly observed in PD [9]. Typically, faces and persons and, less commonly, animals or objects, are reported by the patients. Hallucinations are more common during the wake-sleep transition and in the dark. Hallucinations are associated with cognitive decline, depression, anxiety, sleep-wake disturbances and vivid dreaming [14].

**Cognitive impairment, dementia.** It is important to distinguish mild cognitive impairment from dementia, the latter being present only in a moderate percentage of PD patients. In PD, very subtle cognitive disorders can develop insidiously within the first years of the disease. At this stage, cognitive deficits are not or appear less disabling in the context of daily life but, in a moderate proportion of cases, can progressively increase with the evolution of the disease [6]. Approximately 20%–33% of patients experience mild cognitive impairment already at the time of PD diagnosis, and up to 60%, –80% develop dementia within 12 years of disease duration.[15, 16]. Dementia is a common finding at an advanced stage of PD. Prevalence of dementia among PD patients is present in up to 80% [15].

## B. Sleep disorders in PD

Patients with Parkinson's disease develop a wide range of non-motor symptoms. Sleep disturbance is one of the most common NMS of PD. Though the onset of sleep disorders often precedes the clinical manifestation of mo-

tor symptoms, they are still underestimated. As the main clinical focus is usually put on the motor symptoms of PD, the sleep disturbances often go unnoticed by the clinician. The exact neural correlates of PD sleep problems are not fully understood. Most of the sleep disturbances lead to poor quality of life in patients with PD, which can be improved by the attentive management of these symptoms. [17,18].

### Specific Sleep Disturbances in PD

**Insomnia.** It has three forms: *sleep-onset insomnia* (difficulty in falling asleep), *sleep maintenance insomnia* (difficulty in staying asleep), and *early morning awakenings*. Insomnia is the most commonly observed sleep disorder in PD. The presence of other NMS such as nocturia, depression, and anxiety, and the anticipation of wearing off can also disrupt normal sleep. Contribution of medications such as antihypertensives (atenolol, propranolol, and clonidine), bronchodilators, hormones (thyroxine and estrogen), caffeine, and nicotine to insomnia must always be considered. [17].

**Excessive daytime sleepiness (EDS).** EDS is defined as an inability to maintain wakefulness and alertness during the major waking episodes of the day that results in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep. [18,19]A multifactorial etiology, including the severity of motor symptoms, disrupted nocturnal sleep, and adverse effects of antiparkinsonian medications, especially the dopamine receptor agonists, are contributory. [18] The prevalence of EDS is higher in PD patients than in the general population, with controlled studies showing subjective sleepiness in 34–54% of PD patients compared with 16–19% of controls.[19] Several risk factors for EDS in PD have been identified, and these include male sex, use of dopamine receptor antagonists, insomnia, disability, cognitive impairment, and depression.[19] The use of dopamine receptor agonists has been reported to have an association with sleep attacks in patients with PD [20].

**Rapid eye movement sleep behavior disorder in patients with PD (RBD).** RBD is characterized by abnormal behaviors during REM sleep, especially dream enactments along with heightened muscle tone and/or phasic muscle twitching. The excessive muscle tone during REM sleep often is termed *as REM sleep without atonia*– the central objective finding in RBD [21]. Bed partners of patients with RBD often report various vocalizations and abnormal movements (limb jerks, falling out of bed, and violent assaults), which are parts of dream enactment behaviors. Sometimes, violent limb movements could result in injury to the individual or to their sleep partner. The neuroanatomical substrates of RBD have been reported to be localized in some of the brain stem nuclei [17].

**Restless leg syndrome (RLS).** RLS, also known as Willis-Ekbom disease, is the most commonly observed movement disorder. Its clinical symptomatology includes the urge to move the legs, which is usually accompanied by, or felt to be caused by, uncomfortable and unpleasant

sensations in the legs [17]. RLS, in the absence of any other pathology, is termed as *idiopathic RLS*. *Secondary RLS* occurs in PD, pregnancy, iron deficiency, renal failure, and peripheral neuropathy [22]. It is a sensorimotor neurological disease with an estimated prevalence of 5%–12% [18,19]. Patients of PD with RLS are more likely to have certain NMS such as impulse control disorder, pain, and constipation. In addition, individuals with RLS have a poor quality of life and higher mortality rate compared to those without RLS. Hence, it is important to diagnose and manage this sleep disorder in patients with PD early [17, 22, 23, 24].

**Periodic limb movement in sleep (PLM).** PLMS is characterized by episodes of repetitive stereotypical movements of the lower extremities. It primarily involves a rhythmic extension of the big toe and dorsiflexion of the ankle and occasional flexion of the knee and hip [25]. PLMS may occur independently in patients with PD, it frequently coexists with RLS. Studies have reported a significant association of PLMS with PD, and it is more common in patients with PD of higher duration and severity [25].

**Obstructive sleep apnea in patients with PD (OSA).** OSA is a common finding in patients with PD. However, it is not clear whether OSA is more common in PD compared to the non-PD population [17]. OSA should be promptly diagnosed and treated as it is associated with poor health-related quality of life in patients with PD and others. Several studies have reported higher cognitive dysfunction in patients of PD with OSA compared to those without OSA [25, 26, 27]. Sleep disorders in PD are extremely common, and they may be present as pre-motor symptoms. Their spectrum is large and variable. The exact neural correlates of PD sleep problems are not fully understood. Most of the sleep disturbances lead to poor quality of life in patients with PD, which can be improved by the attentive management of these symptoms. Therefore, the identification and management of sleep disorders in PD is essential. In the majority of the patients, multiple comorbidities may be the primary cause of sleep disturbances, and these should also be carefully managed. Medications can also be a major cause of sleep disorders in PD. In some instances, polysomnography is warranted and helpful. Basic research and clinical studies are needed for better insights into the natural course and treatment options of sleep disorders in PD [17].

### C. Fatigue

Fatigue may be *physiologic* (as a reaction to prolonged or intensive activity) or *pathologic* (the chronic form, induced without or with only minimal exertion, which does not recover with rest) and can be further subdivided into a peripheral and central one. *Peripheral fatigue* represents a loss of muscle strength caused by repeated contractions (called muscle fatigue or physical exercise fatigue). *Central fatigue* is a subjective perception or experience and usually is described as an abnormal degree of tiredness, weakness, or exhaustion that involves both men-

tal and physical domains but in the absence of motor or physical impairment related to the central nervous system. [28]

Fatigue is a nonspecific symptom common to several CNS disorders. According to ICD–10, signs and symptoms of fatigue include asthenia, debility, general physical deterioration, lethargy, and tiredness. Although previously overlooked in PD, fatigue is now accepted to be one of the most common PD symptoms with a reported prevalence between 33% and 58% [29,30]. Fatigue is often considered by patients with PD to be one of the most disabling symptoms affecting daily activities and quality of life [31, 32].

### D. Autonomic disturbances in PD

Autonomic dysfunction is an important non-motor phenotype of Parkinson's disease (6,7). Recently, an increasing number of studies have focused on the role of autonomic dysfunction in the prediction and early diagnosis of PD, making this one of the top research frontiers in the PD field [33, 34, 35, 36].

**Gastrointestinal dysfunction.** The frequency of gastrointestinal symptoms is very high in PD, even during the pre-motor phase of the disease. It has been reported that 88.9% of PD patients will develop gastrointestinal symptoms prior to the onset of PD motor symptoms [33].

**Weight Loss.** Almost half of the PD patients show weight loss during disease progression. However, weight loss can be associated with levodopa usage, rigidity, tremor, and other factors; thus, assessing the frequency of weight loss due to disease progression may be much more accurate during the initial diagnosis of the disease, when patients have not yet started drug therapy [34].

**Drooling of saliva.** Frequent drooling appears in approximately 25% of PD patients. Over 20% of PD patients exhibit diurnal drooling. Drooling causes social embarrassment and increases the risk of aspiration pneumonia; thus, it is a key clinical issue in the management of PD patients [33].

**Dysphagia.** Subjective difficulty swallowing is evident in 30 to 82% of patients with PD; objective abnormalities are present in 75 to 97% of individuals and may be localized to oral, pharyngeal, or esophageal levels. Although typically seen in more advanced PD, dysphagia may become evident early in the course of PD [36].

**Gastroparesis.** The presence of gastroparesis in PD has been documented in multiple studies. Gastroparesis may be present throughout the entire spectrum of PD, including in individuals with the early, untreated disease [37].

**Constipation.** Constipation is variably defined as bowel movements less than three times a week, regular laxative use and/or difficulty during defecation. It is the most frequent lower bowel symptom and can be a major problem in PD. Approximately half of the PD patients have constipation, with increasing severity in the later stages. PD patients have constipation symptoms of 20–70%. Multiple factors may contribute to constipation in

PD; these include reduced water intake, mobility, and disease progression [36].

**Urinary dysfunction.** There are two general categories of urinary symptoms.

**Irritative** symptoms include urgency, frequency, and urge incontinence, in contrast to **obstructive** symptoms, which include hesitancy, reduced urinary stream, straining to urinate, and incomplete emptying [36].

**Sexual dysfunction.** A common presentation of sexual dysfunction in PD patients of both sexes is reduced sexual drive and arousal. Hypersexuality, erectile dysfunction, and ejaculation abnormality occur specifically in male PD patients, while female patients may experience loss of lubrication and involuntary urination during sex. Sexual dysfunction produces an extremely negative influence on the quality of life and emotional moods of PD patients [33].

**Thermoregulatory dysfunction.** Hyperhidrosis, especially nocturnal sweating, is one of the most common features of thermoregulatory dysfunction in PD. Patients with hyperhidrosis usually exhibit higher dysautonomia burden than those without. They also tend to present higher dyskinesia symptoms and have a worse quality of life and higher levels of anxiety and depression [38].

**Cardiovascular dysfunction.** A variety of cardiovascular abnormalities have been described in the setting of PD. Neurogenic orthostatic hypotension (nOH) is the most widely known abnormality, but nocturnal hypertension, supine hypertension, non-dipping, and postprandial hypotension all have been described [36].

**Orthostatic hypotension (OH).** Orthostatic hypotension is a frequent cardiovascular symptom. OH is prevalent in early-stage PD patients. OH may have a negative influence on disease progression and quality of life in PD patients, in whom it increases health care utilization, disrupts cognitive abilities, impairs daily living activities, and increases the rate of medically attended falls. Even in the asymptomatic stage, OH is associated with impaired daily living activities [38].

**Postprandial Hypotension.** Postprandial hypotension can develop within 15 minutes after eating and then may persist for as long as 3 hours [36]. Large, carbohydrate-rich meals are most prone to trigger the phenomenon. Elderly PD patients may be particularly at risk for the development of postprandial hypotension. Constipation, preprandial hypertension at rest, and orthostatic hypotension best predict the presence of postprandial hypotension in elderly PD patients [39].

**Supine Hypertension (SH).** It is defined as a blood pressure greater than 150/90 mm Hg in the supine position. Supine hypertension that occurs at night is also labelled “nocturnal hypertension.” Supine hypertension is associated with an increased risk for the development of stroke, myocardial infarction, and death [40].

## E. Sensory features

Sensory symptoms, and pain, in particular, are common non-motor features of PD. Indeed, virtually all patients with PD experience at least one sensory symptom as part of their prodrome, and such symptoms increase in prevalence and severity with the progression of the disease [41].

**Olfactory deficits.** Hyposmia or anosmia develops in more than 90% of patients with PD, it is usually bilateral and may precede the onset of the dopamine deficiency-related motor features [41]. Although hyposmia is not often reported by patients, the presence or progression of hyposmia could represent a biomarker for early pre-motor PD, particularly if it is combined with other early clinical, imaging and/or biochemical markers, such as reduced noradrenergic denervation of cardiac tissue and cognitive dysfunction [42].

**Visual disturbances.** Visual disturbances, in general, are relatively common in PD with some studies reporting that up to 78% of patients are affected by such disturbances. The incidence of visual hallucinations and diplopia (double vision) in PD increases with disease progression [8].

**Pain and somatosensory disturbances.** Changes in sensory function and onset of pain are a common feature of PD affecting 30–85% of the patient population and remain under-reported. Pain in PD has various causes [41]. Different causative factors of sensory-related symptoms in PD have been identified, some of them having a musculoskeletal origin (for example, causes that result in stiffness, dystonia or muscle cramps), others with a central origin, but primarily related to the neurodegenerative process in PD [7].

## CONCLUSION

Based on clinical and neuropathological data, PD, which was traditionally accepted as a dopaminergic motor disorder, can now be characterized as a multisystem neurodegenerative disease that involves other neurotransmitter systems and affects non-motor functions. NMS are underestimated in contrast to motor symptoms. A range of NMSs are often undeclared, and treatments are inappropriate. It has been recommended during routine consultation of a PD patient, two common errors to be carefully avoided:

(a) to take into account only the clinical neurological status at the moment of examination and not to consider the condition of the patient in daily life;

(b) to take into account only the history and clinical presentation of motor signs, and to miss to look for and evaluate the presence of NMS. The patient themselves can be embarrassed to declare some NMS, such as ICDs or hallucinations. The early identification of non-motor symptoms is not only an important determinant for the quality of life in PD, but offers an additional option for improvement of the therapeutic approach.

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