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Pathophysiology of non-motor signs in Parkinson's disease: some recent updating with brief presentation

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting 1% of the population above sixty years. It is caused by an interaction between genetic and environmental risk factors. Loss of dopaminergic neurons in substantia nigra pars compacta (SNpc) is pathologically characterizing the disease and responsible for the cardinal motor symptoms, most notably, bradykinesia, rest tremors, rigidity, and loss of postural reflexes. Non-motor signs such as olfactory deficits, cognitive impairment, sleep behavior disorders, and gastrointestinal disturbances are reflecting disturbances in the non-dopaminergic system. They precede dopaminergic neuronal degenerations by 5–10 years and are considered the main contributors to patients' disability, particularly after the successful implementation of levodopa (L-dopa) treatment of motor symptoms. The present general review aimed to briefly update non-motor signs and their underlying pathophysiology in PD.

Keywords

Parkinson's disease, non-motor signs, olfactory, depression, sleep disorders, constipation

Introduction

Parkinson's disease (PD) is the second most progressive neurological disorder after Alzheimer's disease (AD) affecting more than 6 million people worldwide [1]. The pathological hallmarks of the disease include the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the presence of eosinophilic protein deposits, Lewy bodies (LBs), in the nigrostriatal region, other aminergic nuclei, and cortical and limbic structures [2]. Also, there is growing evidence that has recently indicated that the pathology of PD includes the peripheral nervous system. The authors suggested that such effect starts from the vagal nerve to the brainstem, and finally to limbic and neocortical brain areas [2].

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Symptomatologically, PD is primarily known as a motor disorder characterized, most notably, by bradykinesia, rest tremors, rigidity, and loss of postural reflexes. These motor symptoms and their positive response to levodopa (L-dopa) treatment are currently considered the major criteria used in the diagnosis of PD in clinical practice [3]. Since 2000, the view of PD as a motor disorder has been changed and recognized as a multisystem neurodegenerative disorder combining both motor and non-motor symptoms [4, 5]. The response of motor signs to L-dopa makes non-motor signs the main contributors to patients' disability in PD. Non-motor signs occur earlier than motor symptoms and their targeted detection can play an important role in the identification of PD patients and in developing novel neuroprotective therapies [5].

The present general review aimed to briefly update non-motor signs in PD and correlate them to their underlying pathological mechanisms.

Non-motor signs in PD

In contrast to motor symptoms which have long been studied since discovery of PD by James Parkinson in 1817, non-motor signs have recently elicited increasing interest [6]. At least, one non-motor sign is exhibited by an overall 98% of patients with PD years or even decades prior to the diagnosis of PD. They often are underdiagnosed and managed more difficulty, increasing with time and always complicating the late stage of the disease [7]. They are attributed to the degeneration of the dopaminergic pathway or other neuronal circuits [7]. Non-motor signs include olfactory dysfunction, neuropsychiatric manifestations, and autonomic dysfunctions [8].

Olfactory dysfunctions

Olfactory dysfunctions, deficits in the sense of smell, in PD have been known as one of the earliest and commonest non-motor signs. It has been described for more than 40 years in 1975 by Ansari and Johnson [9]. Olfactory dysfunction was reported to predate motor symptoms for about four years and presented in about 90% of early-stage PD cases [10]. Recently, they receive much attention as a potentially reliable marker for the preclinical diagnosis of PD. However, some previous studies showed that olfactory dysfunctions are likewise present in other neurodegenerative diseases such as AD, and not specific to PD [11].

Clear underlying pathological mechanisms of olfactory dysfunction in PD are still unraveled. Nonetheless, there is solid evidence attributed this reduced olfactory function to the accumulation of α-synuclein (α-syn) in the olfactory bulb (OB) [12]. In this context, Ross et al. [13] and Beach et al. [14] reported that LBs have been found in the OB, olfactory sensory neurons, and several areas of the olfactory cortices of PD patients. In their study, Hawkes et al. [15] found that LBs were seen in the OB of eight examined PD brains, particularly in the anterior olfactory nucleus. Chen et al. [16] found overexpression of human mutant α-syn (hm-α-syn) in the OB of rats by using adeno-associated virus serotypes 1 or 2 (AAV1/2) viral vector injection, leading to a subsequent decrease of tyrosine hydroxylase (TH) positive cell bodies and fibers in the substantia nigra (SN) after 12 weeks of injection. Doty [10] attributed olfactory dysfunction in PD to a decrease in the number of neurons in locus coeruleus (LC), raphe nuclei, and the nucleus basalis of Meynert. Stevenson et al. [12] observed the presence of α-syn inclusions in non-neuronal cell types including microglia, pericytes, and astrocytes in the anterior olfactory cortex in postmortem human PD patients. α-Syn is detected first in the thin olfactory nerve layer and then the glomeruli of the OB where it can distribute through the dendrites of tufted and mitral cells to other brain areas [17]. In parallel, it is hypothesized that PD-causing agents are obtained from the nasal cavity into the OB, and subsequently, the agent gets access to other brain regions [18].

In summary, olfactory deficits are among the earliest non-motor signs of PD. They seem to be due to the deposition of α-syn in the OB and anterior olfactory nucleus. From there, α-syn spreads by a prion-like mechanism to other brain regions including SN.

Neuropsychiatric manifestations

Neuropsychiatric signs are usually more debilitating than motor symptoms and are considered important causes of excess disability in PD. They are still under-recognized and under-treated in clinical practices, and their diagnosis is challenging despite their frequent occurrence in PD [19]. Neuropsychiatric manifestations

include depression, anxiety, psychosis, apathy and fatigue, sleep disorders, cognitive impairment and dementia, impulse control disorders, and others.

Depression

Based on the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria [20], depression (also called a major depressive disorder) is defined as a mood disorder that causes individuals to feel sadness and loss of interest in daily activities for a period of two weeks, in addition, to fatigue, insomnia, weight loss, etc. Depressive disturbances are common in PD patients with a prevalence of 38% [21]. They can influence many other clinical aspects of the disease including inherent emotional distress, motor and cognitive deficits, functional disability, and other psychiatric comorbidities [22]. They are still, unfortunately, underrecognized and frequently undertreated even when identified [23]. While the underlying mechanisms of depression in PD remain unclear, it is thought to result from a complex interaction of medical, neurobiological, or psychological factors [22].

Neurobiological factors

Depression in PD was reported to be associated with the dysfunction of dopaminergic and non-dopaminergic pathways [24]. The theory of dopaminergic dysfunction is supported by the following observations in depressed PD patients: (1) decreasing availability of dopamine transporter in the striatum [25] that indicates extensive cell loss in the region and increased basal ganglia impairment [26], (2) decreasing dopaminergic and noradrenaline innervation in emotion-related circuitry including the LC, anterior cingulate cortex, thalamus, amygdala and ventral striatum [27] and (3) improvement of depressive symptoms by dopamine agonists [28].

Regarding dysfunction of the non-dopaminergic pathway, noradrenergic and serotoninergic neuronal dysfunctions may also play a role in the development of depression in PD [29]. In this context, Lieberman [30] reported that the activity and number of serotoninergic neurons in the dorsal raphe and of noradrenergic neurons in the LC are decreased. Bohnen et al. [31] and Meyer et al. [32] reported that depressed PD patients showed decreased activity of acetylcholinesterase, a cholinergic marker, in the cerebral cortex, and reduced acetylcholine-receptor binding in the fronto-parieto-occipital lobe and cingulate cortex, respectively. Using the specialized magnetic resonance imaging (MRI) technique, Hemmerle et al. [24] reported that there are significant differences in several brain structures outside the nigrostriatal system between PD patients with and without depression. This includes cingulate and frontal gyruses [33], anterior cingulate and orbitofrontal cortices [34], mediodorsal thalamic nuclei [35], and mediodorsal thalamus [36].

Moreover, there is growing evidence suggesting a genetic contribution to depression in PD [37]. In this context, Arabia et al. [38] found that first-degree relatives of PD patients sometimes show signs of depression at a higher rate indicating a familial susceptibility. Srivastava et al. [37] reported that relatives of early onset PD patients that had heterozygous *PARK2* mutations showed higher depression scores compared to those without mutation in the *PARK2* gene. Menza et al. [39] and Mössner et al. [40] suggested a relationship between depressive symptoms in PD and serotonin transporter gene polymorphism, while, Zhang et al. [41] reported that associations between serotonin or dopamine transporter genes and depression in PD have not been observed.

Medical factors

Some studies link the occurrence of depression to the use of L-dopa in PD patients. For example, Cummings [42] reported that PD patients, who take higher doses of L-dopa for a longer period of time, suffer from depression, while patients stay non-depressed when treated with lower doses of L-dopa. Santamaria and Tolosa [43] found that PD patients treated with L-dopa showed higher depression scores compared with patients not treated with L-dopa when assessed with the Minnesota Multiple Personality Inventory (MMPI). This is because L-dopa may indirectly interfere with serotonergic function in the central nervous system (CNS) [44]. Reversing the effect of L-dopa on serotonin by antidepressants strengthens this suggestion [45]. On the other hand, Choi et al. [46] found that long-term L-dopa therapy did not alter depression disorders in a study involving 34 patients.

Psychological factors

Psychological factors are suggested as relevant underlying mechanisms for depressive disorders in PD [47]. This suggestion is supported by the expression of higher rates of depressive symptoms by PD patients compared to patients with chronic diseases suffering similar disabilities [48]. Higher rates of depressive symptoms in PD patients may be attributed to fears about PD complications and their impact on the quality of life [49]. On the other hand, McDonald et al. [50] argued that depression in PD patients is not attributed to psychological factors but rather to ongoing neurodegeneration.

Anxiety

Anxiety is a common psychiatric sign in PD patients with a prevalence of 20–40% [51]. It can lead to significant impairment of cognitive, functional, motor, and social performance [52]. Common anxiety disorders include social phobia, panic disorder, and generalized anxiety disorder [53]. However, there are several theories explaining the development of anxiety in PD, and clear underlying mechanisms are still out of hand. Anxiety may be returned to combining effects of medical, neurochemical, and psychological mechanisms.

Neurochemical mechanism

Neurochemical alteration was reported to be implicated in the pathophysiology of anxiety [54]. In this context, Martin et al. [55] reported that damage to the subcortical nuclei and disruption of dopamine, norepinephrine, and serotonin [5-hydroxytryptamine (5-HT)] pathways in the basal ganglia-frontal circuits may underlie anxiety in PD. When the authors employed [^{11}C]RTI-32 positron emission tomography (PET) to estimate dopamine and norepinephrine transporter binding in the striatal system, they found that the intensity of anxiety was inversely proportional to the binding of [^{11}C]RTI-32 in the thalamus, amygdala, and LC in PD patients. These findings indicate that anxiety in PD patients might be associated with a loss of both dopaminergic and noradrenergic innervation in the limbic system and LC [27].

Medical mechanism

Implication of PD medications in PD symptoms is still unclear. In this context, it was reported that anxiety is unlikely to be a side effect of L-dopa therapy in PD [53] and 44% of patients with PD showed anxiety before starting L-dopa therapy [56]. On the other hand, panic attacks were reported to be associated with L-dopa treatment particularly in off-periods following declining L-dopa levels in the brain [57, 58]. Likewise, some authors reported that the use of dopamine agonists did not affect anxiety degree in PD patients and others reported the opposite results. For instance, Menza et al. [53] reported that treatment of PD patients with pergolide did not affect anxiety. On the other hand, Lang et al. [59] found that anxiety was seen in 5 patients out of 26 patients treated with pergolide.

Psychological mechanisms

Anxiety may occur as a reactive response to the diagnosis of patients with PD [52]. In consistency, anxiety in PD patients was more severe when compared with anxiety disorder resulting from chronic illnesses and similar disabilities in non-PD patients [57]. However, PD patients are at greater risk of developing anxiety before the diagnosis of PD suggesting that anxiety may be an early non-motor signs in PD patients [60].

Sleep disorders

Sleep disorders in PD patients are common and negatively affect patients' quality of life and worsen their symptoms [61]. They affect more than half of PD patients with a prevalence of 2–3.5 times more than in healthy individuals [62]. Common sleep disorders in PD patients are excessive daytime sleepiness (EDS), rapid eye movement sleep behavior disorder (RBD), and insomnia [63]. However, most of the sleep disorders that occur late in the course of PD, RBD, and EDS can be seen earlier even before motor signs [64]. Generally, sleep disorders in PD may be caused as the result of some motor and nonmotor symptoms, some medication, and degenerative changes in the brainstem [65].

RBD

RBD is a parasomnia characterized by loss of muscle atonia and the occurrence of abnormal behaviors such as dream-related vocalizations (e.g., talking, screaming, and shouting) and/or complex motor movement (e.g., punching and kicking) [66]. Most recent meta-analysis studies reported that the prevalence of RBD signs in PD was 23.6% compared to 3.4% in control individuals [67]. Signs of RBD can occur in every stage of the disease even before the diagnosis of PD [62]. RBD was reported to be caused by LB pathology in PD affecting the brain stem structures that play a role in the regulation of rapid eye movement sleep [68].

Insomnia in PD

Insomnia is a common sleep disorder in PD that affects about 60% of PD patients [69]. It is defined as a difficulty in sleep initiation, sleep maintenance problem, or early awakening (e.g., short duration) [70]. Sleep fragmentation is among the most common sleep complaints [71]. It is known as an impairment of sleep integrity (i.e. interruption of night sleep resulting in lighter sleep or wakefulness) [63].

The etiology of insomnia in PD is multifactorial [72]. Coe et al. [62] stated that neuronal damage in the brain regions associated with sleep plays an essential role in insomnia. In addition, primary sleep disorders such as altered dream phenomena, restless leg syndrome (RLS), RBD, and periodic leg movement in sleep (PLMS), as well as PD-related symptoms including movement symptoms (e.g., nocturnal akinesia, tremor, and rigidity) and non-motor signs (e.g., psychiatric comorbidities such as anxiety), are contributing to the pathogenesis of insomnia in PD [73]. Medically, drug-disease interaction was reported to be associated with insomnia in PD patients. For example, Gómez-Esteban et al. [71] found that wearing-off of dopaminergic medication overnight may lead to insomnia. Chahine et al. [74] reported that dopamine receptor 1 (D1) and D2 activation by higher doses of dopaminergic medications at bedtime is correlated with poor sleep quality.

EDS

EDS is chronic or episodic sleepiness that occurs during the day in PD patients [63]. It was reported that EDS occurs in 55% of PD patients compared to 16–19% of control individuals [75]. EDS was also reported to be a possible risk factor for the future development of PD [76]. EDS in PD is attributable to disruption of the quality of night sleep, neurodegeneration in brain areas responsible for sleep and wake, and antiparkinsonian medications [77].

Deterioration of night sleep quality was reported to be associated with RBD [78] and RLS [79]. However, some studies demonstrated no difference in subjective sleepiness between PD patients with or without RBD and RLS [80]. Moreover, the deterioration of night sleep quality can be produced by anxiety and depression, and cognitive dysfunction in PD patients [63].

Degeneration of neurons controlling wakefulness and sleep could lead to sleep disorders including EDS [81]. Moreover, some studies linked polymorphism in the catechol *O*-methyltransferase (COMT) *val158met* gene and the intron in the gene encoding phosphodiesterase 4D (PDE4D) which affect synaptic dopamine levels and memory consolidation, respectively, to EDS [82, 83].

Dopaminergic medications were shown to produce sleep attacks in PD patients. In this context, there are several studies the demonstrated that dopamine agonists or L-dopa are associated with increased daytime sleepiness in PD patients [84]. However several other studies showed no significant association [85]. Moreover, some studies revealed that EDS was significantly worsened in drug-naïve PD patients compared to control individuals [86] and some other studies failed to show a significant difference in EDS between newly diagnosed PD and control [87].

Psychosis

In brief, psychosis is defined as a loss of reality, and in PD; it takes the forms of hallucinations and/or other psychotic disturbances such as illusions or delusions [88]. It is considered one of the most frequent and disabling non-motor signs in PD with a prevalence of 20–70% in advanced disease stages [89]. Among psychotic signs, visual hallucination is the most common in PD and occurs frequently in dim light or at the

end of the day [90]. It is classified into formed and minor variants: formed visual hallucinations include various contents such as persons, animals, or objects while minor hallucinations include illusions such as the presence or passage of an object [91]. Both variants are present in 22.2% and 25.5% of PD patients [88].

In PD patients, auditory hallucinations occur less frequently than visual hallucinations. They are usually occurring in the form of indistinct sounds, e.g., radio sound in the room, music playing on the street, or talking outside the room [92].

Delusions are supposed to be associated with disease progression and cognitive impairment [93]. In a study comparing isolated delusions and delusions with hallucinations, Warren et al. [93] found that delusions were primarily paranoid in nature (83% of cases).

The risk factors for the development of PD psychosis include older age, longer duration of illness, greater severity of illness, dementia, delirium or depression, sleep disorders, and use of dopaminergic agonists [94].

The underlying mechanisms of PD psychosis remain poorly understood and it may result from the interplay of neuronal degeneration, and abnormalities in neurochemical transmitters and neural structures [88]. In this context, Samudra et al. [88] reported that visual hallucinations may be resulted from excessive stimulation of striatal/mesolimbic dopamine receptors. In consistency, Thanvi et al. [95] found that stimulation of dopamine receptors by the dopamine agonist, amphetamine, produced psychosis, and blocking of dopamine receptors by antipsychotics relieves psychosis. Bosboom et al. [96] reported that loss of cholinergic neurons and subsequent cholinergic deficits may be associated with visual hallucinations in PD psychosis. Klawans and Ringel [97] reported that degeneration of some of the 5-HT pathways may play an important role in PD psychosis. The authors stated that the improvement of psychosis with the 5-HT3 receptor antagonist, ondansetron, and neuroleptics that have blocking effects on serotonin and dopamine receptors support the concept [97]. Structurally, Sanchez-Castaneda et al. [98] found a significant reduction in the volume of grey matter in the lingual gyrus and superior parietal lobe, regions involved in higher-order visual processing, in PD patients with hallucinations compared to non-hallucinating patients. Ibarretxe-Bilbao et al. [99] also observed hippocampal atrophy in PD patients with hallucinations. Moreover, it was reported that abnormalities of visual processing may be implicated in the generation of hallucinations [100]. Using functional MRI, Stebbins et al. [101] found that PD patients with hallucination showed visual stimulation as the result of frontal and subcortical activation and a decreased cerebral activation in the occipital, parietal, and temporal-parietal areas compared to the non-hallucinator patients.

At the metabolic level, it was reported that decreased perfusion, glucose metabolism, and blood flow to some brain regions can be associated with PD hallucinations. For instance, Okada et al. [102] found that decreased glucose metabolism in the posterior brain region was seen in PD patients with hallucination by the aid of single photon emission computed tomography (SPECT) or PET. The authors also observed a decrease in the flow of cerebral blood to the left temporal and temporal-occipital lobes in hallucinating PD patients [102].

Genetically, multiple studies showed the association in the polymorphism of several genes including apolipoprotein E, cholecystokinin system, dopamine receptors and transporters, serotonin, COMT, angiotensin converting enzyme and tau, and hallucinations in PD [103].

Apathy

Apathy is a common neuropsychiatric sign in PD patients with a prevalence of 39.8% [104]. It is identified as a lack of goal-directed behavior because of a reduction of feeling, interest, emotional reactivity, and motivation [105]. The definite physiopathological mechanism mediating the occurrence of apathetic symptoms in PD is still unclear. However, compromising of the basal ganglia was reported as a major contributing factor [106]. In addition, Dujardin et al. [107] reported that dementia, depression, and disease progression can play a role in the development of apathetic symptoms. Also, Braak et al. [108] found that defects in the mesocorticolimbic system and reward processing are proposed as an etiopathogenic factor for apathy in PD. Apathy has a major impact on the patients' quality of life and caregivers. Clinical differentiation of apathetic symptoms from symptoms of depression may help in finding individual treatment approaches for apathetic symptoms [109].

Fatigue

Fatigue is a common non-motor symptom with a prevalence of 33–80% in PD patients. It can be defined as an excessive sense of tiredness, lack of energy, weakness, and exhaustion (subjective fatigue) or as a loss of correspondence between efforts and performances (objective fatigue) [110]. One-third of patients see fatigue as the most disabling symptom that worsens their quality of life [111].

There is much evidence that suggests that fatigue is a primary manifestation rather than a secondary symptom. This suggestion is supported by the findings of Schrag et al. [112] who reported that fatigue is not associated with motor signs and disease progression in most patients, respectively. Moreover, the absence of such an association supports the hypothesis that fatigue in PD may result from the disruption of non-dopaminergic pathways [113]. Primary pathophysiological mechanisms of fatigue in PD may include chronic neuroinflammation [114], altered monoaminergic neurotransmission, and hypothalamic-pituitary-adrenal axis [115]. On the other hand, some studies indicated that fatigue can be associated with depression, sleep disorders, apathy, and anxiety [116], worsened with disease progression [117] and present in one-third of drug-naive patients in the initial motor stage of the disease [118]. Moreover, Kluger and Friedman [119] found that fatigue may occur as a homeostatic mechanism to control energy utilization. Taken together, investigation of the definite underlying mechanisms of fatigue can help in finding therapeutic approaches that control this important non-motor sign.

Cognitive impairment

Cognitive impairment is the most common among non-motor signs leading to a significant reduction in the quality of life [120]. Cognitive impairment varies from subjective cognitive decline (SCD) to mild cognitive impairment (MCI) to PD dementia (PDD) [121].

SCD

In the SCD group, cognitive decline is usually noted by the patients, family members, or health personnel with a prevalence of 28.1% in *de novo* PD cohort [122], while cognitive test performance is in the normal range. SCD was reported to be associated with an increased risk of future cognitive decline [123].

MCI

MCI occurs in approximately 14.8–42.5 % of PD patients and is evident in 10–20% of patients at the time of diagnosis [124]. Cognitive deficits in MCI can be detected by various neuropsychological observations but do not significantly disrupt daily living [121]. In which, the most affected domains are executive, memory, visuospatial, attention tasks, and less frequent language impairment [125]. MCI may develop into dementia but some PD-MCI patients remain stable and others can revert to normal cognition [126].

PDD

PDD affects up to 90% of patients [127]. PDD results in a more devastating cognitive impairment, affects more than one area of cognition, and significantly impairs daily activities [121]. PDD involves executive, visuospatial, attention, and memory impairment; with the language usually preserved [128]. However, little is known about the mechanisms mediating cognitive decline in PD, symptoms probably occur as the result of changes in neuronal integrity, neurochemical deficits, cerebro-vascular pathology, and others.

Pathologically, degeneration of the nucleus basalis of Meynert precedes and can predict the onset of cognitive impairment [129]. The authors also observed decreasing the volume of grey matter and increasing diffusivity in the nucleus basalis of Meynert in PD with cognitive impairment compared to patients without impairment [130].

LB pathology in different brain regions was seen as an important correlate of cognitive decline in PD [123]. In this context, Hely et al. [130] suggested that cortical and limbic involvement by LB and Lewy neurites are the dominant changes in PDD. Smith et al. [131] showed that α-syn pathology extended to the limbic system or neocortex in a study including 41 autopsies from pathologically verified PD cases with dementia and these changes were more frequent than in non-demented PD patients. In addition, amyloid plaque pathology was evidenced as a significant contributor to one-third of patients with PDD [123]. In consistency, Painous and

Marti [132] reported that LB-type pathologies frequently coexist suggesting an interaction between α-syn, tau, and amyloid-β (Aβ) proteins aggregates. The authors also showed in the combined Lewy-Alzheimer transgenic mice models that the interaction between the three proteins resulted in the acceleration of neuropathology and cognitive decline [133].

Changes in cortical synapses can affect cognition in PD [123]. Whitfield et al. [134] and Bereczki et al. [135] found that reduced levels of zinc transporter 3, a marker of synaptic plasticity, and two key synaptic proteins, neurogranin and synaptosomal associated protein 25, are associated with cognition in PD. Neurogranin levels were found to be increased in cerebrospinal fluid (CSF) in PD patients with cognitive decline [135]. Due to that, it can act as a potential biomarker to predict future cognitive decline [123].

Neurochemically, the dopaminergic system was reported to contribute to some of the cognitive problems in PD. For example, Christopher et al. [136] revealed that executive dysfunction has been associated with the deficiency of striatal dopamine and D2 receptors in the insula lobe region in PD-MCI patients. Christopher et al. [137] showed that PD patients with memory impairment had a significant reduction in the binding activity to D2 receptors in the regions of the insular cortex, parahippocampal gyrus, and anterior cingulate cortex compared to patients without cognitive impairment.

Besides the dopaminergic system, there is growing evidence indicating that a number of non-dopaminergic neurotransmitter systems may contribute to cognitive decline in PD [138]. Of which, the cholinergic system is affected early in PD and contributes to cognitive decline [123]. In this context, it was reported that there were greater reductions of choline acetyltransferase activity in the hippocampal, prefrontal, and temporal cortex in PDD than in non-demented PD patients [139]. Moreover, Vorovenci and Antonini [140] and Ko et al. [141] showed that increased activity of adenosine A_{2A} receptors expressed by striatal gamma-aminobutyric acid (GABA)-ergic neurons located in the thalamus and neocortex is associated with worsening of cognition. Aarsland et al. [123] demonstrated that monoaminergic nuclei as serotonergic raphe and noradrenergic LC nuclei may affect cognitive activity in PD patients. This is attributable to their effects on the activity of the synaptic network.

Other factors such as cerebrovascular pathology, mitochondrial alteration, and neuroinflammation may play a role in cognitive decline in PD. Compta et al. [142] reported that parietal occipital white matter hyperintensities were associated with PDD and can predict longitudinal cognitive decline among patients with MCI. However, Schwartz et al. [143] stated that there is no correlation between the severity of subcortical small vessel diseases and PDD. Mitochondria are crucial for synaptic activities and a relationship between α-syn and mitochondrial activities is well-known [123]. In a postmortem study, Gatt et al. [144] found that mitochondrial complex I deficiency and decreased levels of mitochondrial DNA in the prefrontal cortex occur excessively in PDD than in patients without dementia. Neuroinflammation was reported to have an implication on cognitive decline in PD [145], and increased levels of CSF cytokines are found to be associated with cognitive impairment in PD [146]. Moreover in an imaging study, Petrou et al. [147] showed an association between diabetes, loss of grey matter, and cognitive impairment in PD.

Autonomic dysfunctions

Autonomic dysfunctions are an important group of non-motor signs in PD. They have been recognized since discovering the disease [148]. Recently, there is increasing evidence that autonomic dysfunctions have an important role in the early prediction and diagnosis of PD. Autonomic dysfunctions include urinary and sexual dysfunction, cardiovascular dysregulation, gastrointestinal disturbances, pupillo-motor and tear abnormalities, and thermoregulatory aberrance [149].

Orthostatic hypotension

Orthostatic hypotension (OH) is a common cardiovascular symptom of PD [148]. It is defined as a decrease in systolic blood pressure by ≥ 20 mmHg [1 mmHg = 133.322 pascals (Pa)] or in diastolic blood pressure by ≥ 10 mmHg on standing [150]. The estimated prevalence of OH is about 30% in PD [151] and 40% in early stage PD patients [152]. OH affects negatively patients' quality of life as it disrupts cognitive abilities and increases health care utilization [153]. Clinical signs associated with OH are caused by the reduction

of blood flow to different body organs particularly the brain. Cerebral hypoperfusion with blood can lead to visual disturbances, dizziness, transient cognitive impairment, and loss of consciousness (syncope). In general, OH may result in fatigue, chest pain, dyspnea, and falls [154]. The mechanisms of OH in PD can be centrally mediated by degeneration of brain autonomic centers or peripherally resulting from post-ganglionic lesions [155]. Some antiparkinsonian drugs are reported to cause OH. For instance, it was reported that L-dopa [156], some dopamine agonists [157], and monoamine oxidase (MAO-β) inhibitors such as rasagiline and selegiline [158] have been recognized as a potential factor for inducing OH.

Bladder disturbances

Micturition centers in the pons and frontal lobe control bladder emptying by both reflexive and voluntary mechanisms. During filling, relaxation of the bladder wall and contraction of the internal sphincter is maintained by the sympathetic nervous system. On the other hand, bladder contraction and relaxation of the internal sphincter as well as reciprocal inhibition of the sympathetic nervous system are controlled by the pontine micturition center during the voiding stage [159].

Urinary dysfunctions are common in PD with a prevalence of more than 50% [160] and usually occur after the development of motor symptoms [161]. Bladder dysfunctions in PD patients are manifested by symptoms of incontinence and retention. Incontinence symptoms are more common and include frequency, nocturnal urine, and urgency. Retention-based signs consist of decreased urinary stream, intermittent stream, straining to void, and sensation of incomplete emptying [161].

Bladder dysfunction in PD was reported to result from impairment of the frontal basal ganglia D1 dopaminergic circuit which controls the lower sacral micturition reflex. This alteration leads to the disinhibition of the micturition reflex which results in detrusor overactivity and overactive bladder symptoms [161]. Degenerative changes in the brainstem nuclei including the pontine micturition and continence centers may be associated with symptoms of bladder storage in PD. This may be because urinary functions are coordinated by the pontine micturition and continence centers in lower brainstem nuclei [162]. Moreover, Kitta et al. [163] found in a PET study that periaqueductal grey, supplementary motor area, cerebellar vermis, insula, putamen, and thalamus are activated during detrusor overactivity in PD.

Sexual dysfunction

Sexual dysfunction is common in PD and is usually associated with depression [164]. Raciti et al. [165] reported that 68% and 53% of men and women with PD complained sexual dysfunction. Sexual dysfunction has a major impact on the quality of life of PD patients [166]. In men, the most prevalent sexual dysfunctions include erectile dysfunction [167], premature ejaculation [168], and decreased desire [169]. In women, common sexual disorders include a decrease in sexual life, low sexual desire, arousal and lubrication problems, and orgasmic difficulties [167]. Sexual behavior is a multifactorial process requiring coordination between person's mental, autonomic, sensory, and motor systems. The sexual process is also depending on the proper function of the neurologic, vascular, and endocrine systems. Many of these aspects can be disrupted in PD patient's particularly physical and mental systems [169]. In addition, testosterone deficiency is another possible explanation for lower sexual interest in men suffering from PD [170]. Orgasmic dysfunction in men, vaginal tightness, and urinary incontinence in women increase depression in PD patients [171]. But also increased sexuality was reported (sexual preoccupation behavior) [172]. Sexual desire discrepancy, in which the frequent demands for sex by patients, mainly men, was reported to be created by restoring desire after the initiation of antiparkinsonian therapy with dopaminergic agents and decreased desire in the partner associated with burden and depression [173].

Gastrointestinal symptoms

Gastrointestinal dysfunctions are the commonest among autonomic nervous system impairments [174] and could be considered as earlier biomarkers for PD [175]. They have been reported to occur in 60–80% of patients and greatly affect patients' quality of life [176]. Moreover, gastrointestinal disorders in PD patients are common causes of emergency admission. Also, they can cause severe complications including malnutrition, intestinal obstruction and intestinal perforation, megacolon, and pulmonary aspiration [177].

The most common gastrointestinal disorders in PD include sialorrhea, dysphagia, gastroparesis, small intestine bacterial overgrowth (SIBO), and constipation.

Sialorrhea

Sialorrhea, excessive salivation, is a common symptom in PD affecting about 10–84% of patients [178]. Drooling affects the quality of life of both patients and carers [179]. Production of saliva in PD was reported to be unchanged and drooling seems to occur as the result of (1) dysphagia with infrequent swallowing of saliva [180], (2) facial muscle rigidity with lingual bradykinesia and depression of swallowing efficiency [181], and (3) cognitive problems [178].

Dysphagia

Dysphagia occurs in about 11–81% of patients with PD and increases with the disease progression [182]. Swallowing impairment reduces patients' quality of life, affects the intake of medications, and can lead to aspiration pneumonia and malnutrition [183]. The pathophysiology of dysphagia in PD is complex and involves both dopaminergic and non-dopaminergic mechanisms [184]. In this context, Polychronis et al. [185] stated that dysfunction of the dopaminergic neural network may affect the supramedullary swallowing system and cause dysphagia in PD. Mu et al. [186] reported that LBs in non-dopaminergic brain areas and α-syn in peripheral motor and sensory nerves innervating the pharyngeal muscles might be implicated in dysphagia in PD. Schröder et al. [187] correlated reduced concentration of substance P, a neuropeptide with a lot of functions but also associated with cough and swallowing reflex, to the occurrence of dysphagia in PD patients.

Gastroparesis

Gastroparesis is a long-term condition characterized by the presence of stomach fullness and inability to complete meals for about 12 weeks together with delayed gastric emptying according to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). In addition, scintigraphy and upper gastrointestinal endoscopy revealed no obstructive lesions [188]. It is a common symptom in PD, observed in about 70–100% of patients, and may occur in both early and advanced stages of the disease [189]. Gastroparesis affects the nutritional status and quality of life of PD patients. Moreover, it may lead to inadequate absorption of oral anti-PD medications resulting in response fluctuations [190]. So far, the pathophysiology of gastric dysmotility has not been understood well. However, Heimrich et al. [191] found that functional deficits in gastric pacemaker cells (interstitial cells of Cajal) were not responsible for changes in gastric motility in PD by using an electromagnetic capsule system. The authors returned gastroparesis in PD to disturbances in neurohumoral signals via the vagus nerve and myenteric plexus [191]. It was also reported that some anti-PD medications such as L-dopa can lead to the development of delayed gastric emptying [188].

SIBO

SIBO is known as the presence of an extraordinary number of bacteria in the small intestine [153]. Its prevalence in PD patients ranges in some recent studies from 54% to 67% [190]. While Gabrielli et al. [190] postulated that SIBO may be resulted from impaired gut motility, Gibson and Barrett [192] reported that SIBO may itself increase gut motility and lead to less severe constipation and tenesmus. This could be explained by the exposure of the intestinal wall to bacterial metabolites and toxins which increase intestinal motility [192].

Constipation

Constipation is known as a decrease in the bowel movement to less than three movements a week. It is considered one of the most common gastrointestinal symptoms in PD patients affecting about 50–80% of patients. Constipation often occurs early in PD and may precede motor symptoms by several years [193]. Underlying mechanisms of constipation in PD seem to be multifactorial. Besides risk factors such as physical weakness and lifestyle risks such as reduced fluid intake and medication side effects [194], disease-related pathomechanisms include slow intestinal transit and outlet obstruction [195]. Dysregulation of the central

and peripheral parasympathetic system was reported as a cause of delayed colonic transit [196]. Also, alteration in the sacral parasympathetic nuclei and pelvic ganglia may enhance outlet obstruction [196]. Also, α-synucleopathy in the autonomic nervous system innervating the gastrointestinal tract and enteric system of the colon, and neuronal loss in the mesenteric and submucosal plexi were implicated in constipation in PD [155].

Other signs

Weight loss

Compared to healthy controls, many studies revealed that PD patients showed lower body mass index (BMI) with a prevalence of 11.6 [197]. It was reported to occur earlier in the disease preceding motor signs [4]. The etiology seems to be multifactorial including hyposmia, dyskinesias, gastrointestinal disorders such as difficulty chewing, dysphagia, intestinal hypomotility, nausea, depression, apathy, medication side effects, and increased energy consumption due to involuntary movements, and muscular rigidity [198]. In addition, weight loss in PD patients may be related to intrinsic physiological changes of neurodegeneration. In this context, Munhoz and Ribas [199] found that PD patients with weight loss showed lower levels of leptin and insulin-like growth factor type 1 (IGF-1) compared to PD patients without weight loss. Weight loss is generally associated with poor quality of life and health that can lead to rapid PD progression [200].

Pain

Pain is a common non-motor sign in PD and approximately 30–50% of patients complained of pain during the course of the disease [201]. Classification of pain is complex and the most commonly used classification system in clinical practice is Ford's classification. Ford's classification includes musculoskeletal, dystonic, neuropathic/radicular, central or primary, and akathisia. It utilizes an approach that involves the cause of pain and its relation to the motor symptoms [202]. Musculoskeletal pain is the most common type and is associated with bradykinesia, and muscle rigidity [203]. Dystonic pain is associated with sustained or intermittent muscle contractions. Its occurrence in the early morning or as a wearing off phenomenon indicates dopaminergic deficiency [202]. Neuropathic/radicular pain is a much localized pain that limited to a nerve or nerve root territory and has neuropathic characteristics such as burning, paresthesia, and electric-shock like [204]. It is thought to be associated with focal compression that occurs with degenerative joint disease in most PD patients [202]. Central or primary pain has neuropathic characteristics and may occur as the result of impaired central modulation of pain due to dopaminergic deficiency in the basal ganglia [205]. Akathisia is an inner restless feeling and inability to remain still with a desire to move or change position. It is suggested that akathisia results from dopamine dysfunction in the dopaminergic mesocorticolimbic pathway [206]. Pain results from both central and peripheral mechanisms. Central mechanisms consist of altered pain processing, lower pain threshold, and motor/non-motor fluctuations. Altered inflammatory signals and L-dopa-induced vitamin B12 deficiency comprise peripheral mechanisms [207]. In addition, polymorphism in genes that increase pain susceptibility may play a role in the occurrence of pain in PD [208]. Polyneuropathy could occur in patients treated with high doses of L-dopa in an advanced stage of the disease [209]. Pain in PD disease also can be associated with a number of other non-motor signs including depression, sleep, and autonomic symptoms [210].

The discussed non-motor signs were listed with their prevalence and references in Table 1.

Table 1. Non-motor signs in PD and their prevalence

Non-motor signs	Prevalence in PD patients	Reference
Olfactory dysfunction	90% of early stage PD cases	[10]
Neuropsychiatric manifestations		
Depression	40–55%	[21]
Anxiety	20–40%	[51]
Sleep disorders		
RBD	23.6%	[41]
Insomnia	55%	[69]

Table 1. Non-motor signs in PD and their prevalence (*continued*)

Non-motor signs	Prevalence in PD patients	Reference
EDS	55%	[75]
Psychosis	20–70%	[89]
Apathy	39.8%	[104]
Fatigue	33–80%	[110]
Cognitive impairment		
SCS	28.1%	[122]
MCI	25–30%	[124]
PDD	90%	[127]
Autonomic dysfunctions		
OH	30–40%	[151]
Bladder disturbances	50%	[160]
Sexual dysfunction	68% in men and 53% in women	[165]
Gastrointestinal disturbances		
Sialorrhea	10–84%	[178]
Dysphagia	11–81%	[182]
Gastroparesis	70–100%	[188]
Small intestine bacterial over growth	54–67%	[190]
Constipation	5–80%	[193]
Others		
Weight loss	11.6%	[196]
Pain	30–50%	[201]

Conclusion

However, PD has been recognized as a motor disease since its discovery, it is now recognized as a multisystem disorder combining both motor and non-motor signs. Non-motor signs are usually attributed to neurobiological, medical and psychological factors. Their impact is greater than motor signs particularly in the late stage of the disease. Research on how to diagnose and control non-motor signs is of great importance to improve patients' quality of life.

Abbreviations

5-HT: 5-hydroxytryptamine

D2: dopamine receptor 2

EDS: excessive daytime sleepiness

L-dopa: levodopa

LBs: Lewy bodies

LC: locus coeruleus

MCI: mild cognitive impairment

OB: olfactory bulb

OH: orthostatic hypotension

PD: Parkinson's disease

PDD: Parkinson's disease dementia

PET: positron emission tomography

RBD: rapid eye movement sleep behavior disorder

RLS: restless leg syndrome

SCD: subjective cognitive decline

SIBO: small intestine bacterial overgrowth

α-syn: α-synuclein

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Author contributions

KR: Conceptualization, Writing—original draft, Writing—review & editing. RM: Conceptualization, Writing—original draft, Writing—review & editing. CK: Software, Writing—original draft. BK: Software, Writing—original draft. WDR: Conceptualization, Supervision, Validation.

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The authors declare that they have no conflicts of interest.

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