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The Non-Motor Prodromal Symptoms of Parkinson's Disease: A Review

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ABSTRACT

Parkinson's disease is a common progressive neurodegenerative disorder with both motor and non-motor symptoms. There is no clear etiology, and it has no cure. The non-motor features often precede the motor symptoms by many years, so they are considered prodromal symptoms of the disease. These symptoms include olfactory dysfunction, constipation, sleep problems, and depression. The purpose of this study is to review the literature on Parkinson's disease non-motor prodromal symptoms and their role from the early stages throughout the disease's development. The review discusses several aspects related to the prodromal features of Parkinson's disease: their prevalence in Parkinson's disease patients, the pathophysiology, the treatment, if it is possible, and the prodromal symptoms' effect on the diagnosis, prognosis, and management of the disease, in addition to their impact on patients' quality of life. More studies are required to precisely pinpoint the timing of non-motor prodromal symptoms onset and modify the diagnostic criteria for Parkinson's disease accordingly.

KEYWORDS

constipation, depression, gastrointestinal dysfunctions, hyposmia, olfactory dysfunction, sleep disturbances

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1. Introduction

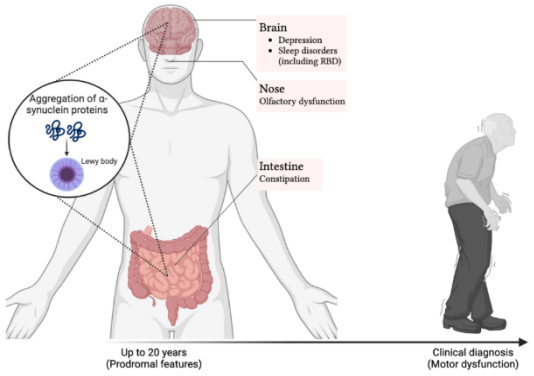
Parkinson's disease (PD) is considered the most frequent neurodegenerative movement disorder, affecting 2% to 3% of people aged over 65 years old (Balestrino and Schapira, 2020; Poewe et al., 2017). It is also a common factor of morbidity that influences 1 to 2 per 1000 people at any time and impacts 10 million individuals worldwide (Bang et al., 2021; Tysnes and Storstein, 2017). Recently, due to the aging population, the number of PD sufferers has significantly risen; this is described as a PD pandemic (Murakami et al., 2023).

In most cases, the etiology of PD is not fully clear. There are many pathological markers of the disease. For instance, degeneration of dopaminergic neurons in substania nigra pars compacta (Chen et al., 2023; Sandeep et al., 2023), and Lewy body (LB) pathology (which is intracellular inclusions of an abnormal protein called α-synuclein) (Balestrino and Schapira, 2020; Smith et al., 2023). α-synuclein may contribute to neurodegeneration in PD via numerous intracellular dysfunctions, such as mitochondria and lysosome impairments, as well as through changing calcium normal function (Calabresi et al., 2023).

Clinically, PD is a progressive disease characterized by motor and non-motor features (Church, 2021; Murakami et al., 2023). Even though the non-motor symptoms often happen many years before the motor dysfunction (Dong-Chen et al., 2023; Schapira, Chaudhuri, and Jenner, 2017), the diagnosis of PD still depends on the occurrence of the motor symptoms, which are bradykinesia, rigidity, and tremor (Schapira et al., 2017). Non-motor features have recently received much attention in identifying people in the prodromal stage of PD (Taguchi et al., 2020; Tysnes and Storstein, 2017). The most significant prodromal symptoms are olfactory dysfunction (OD), constipation, rapid eye movement (REM) sleep behavior disorder (RBD), and depression (Schapira et al., 2017). The former symptoms impact the patient's quality of life more than the classic motor ones (Marinus et al., 2018). Additionally, essential biomarkers could predict the disease's clinical onset (Bang et al., 2021; Basellini et al., 2023). RBD was found to have the strongest predictive value for PD, while hyposmia, constipation, and mood disorders were sensitive but not specific when evaluated individually (Mantri and Morley, 2018).

Patients with two or more prodromal symptoms exhibit greater indications on the PD screening questionnaire than those with none or only one symptom (Roos et al., 2022). The presence of more than two prodromal symptoms increased the probability of developing PD by four times compared to having just one symptom (Mantri and Morley, 2018). Furthermore, the prodromal non-motor symptoms of PD could be helpful in the early diagnosis of the disease and could provide better management and prognosis (Bang et al., 2021). One study showed that 11% of PD patients with multiple non-motor features reported a worse prognosis, as they experienced more motor symptoms and daily life obstacles (Roos et al., 2022) (Figure 1).

Figure 1: Prodromal non-motor symptoms of Parkinson's disease. Non-motor features may precede the onset of classic motor dysfunction for many years. α-synuclein pathology affects various nervous system regions, leading to non-motor and motor symptoms. Though motor abnormalities are the key to diagnosing the disease, non-motor ones may impact the patient's quality of life for many years before that. Therefore, more attention to the prodromal stage is needed to manage the condition better.



In this review, we discuss PD's prodromal symptoms and highlight their role in the early stages of the disease.

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2. Discussion

2.1. Olfactory Dysfunction and Parkinson's Disease

OD, or hyposmia, refers to a decreased sense of smell, which can simply affect the daily routine of one's diet and nutrition or even threaten everyday safety (Chase and Markopoulou, 2020).

Although OD can be a manifestation of aging and several disorders, it is widely cited as one of the first and most prominent non-motor symptoms of PD that develops in 50%–90% of patients (Chase and Markopoulou, 2020; Fullard et al., 2017). It usually appears in the early phase of PD up to four years prior to the onset of classic motor features (Chase and Markopoulou, 2020).

The pathogenesis behind PD-related OD is not yet fully understood; the LB pathology is suspected to lead the main process, in which abnormal deposits of α-synuclein in the neurons of the olfactory bulb (OB) cause the neurodegeneration. Braak's hypothesis tried to explain the early onset of OD preceding the motor symptoms, suggesting that a pathogen enters the nasal cavity and affects the neurons of the OB, leading to α-synuclein pathology, which in turn spreads through the olfactory tract toward the central nervous system to eventually reach the dopaminergic neurons of the substantia nigra that triggers the motor dysfunction. Although this hypothesis was supported by many studies, not all PD patients follow the same pattern (Rietdijk et al., 2017). With a similar mechanism, environmental toxins (pesticides, air pollutants, metals) were suggested as possible preventable agents that may initiate the pathology (Chen et al., 2022).

Dysregulating neurotransmitters such as dopamine, serotonin, and acetylcholine also play a role in OD (Marin et al., 2018). As dopamine deficiency is strongly associated with classic PD motor symptoms, it is worth mentioning that the dopamine mechanism of action in the OB is different and not well-specified; the number of dopaminergic neurons seems to be increased in the OB's glomerular layer, and no improvement in olfaction was noticed after dopamine replacement therapy. On the other hand, as the OB is enriched with nicotinic acetylcholine receptors, studies revealed that nicotine may have the potential to ameliorate PD-related hyposmia. Interestingly, smokers showed better olfaction compared to non-smokers among PD patients (Bang et al., 2021). However, more studies are needed to better understand the pathology.

Although PD-related hyposmia usually presents bilaterally (Schapira et al., 2017), more than 75% of patients seem not to recognize their olfactory impairment before testing with olfaction-evaluating tools such as odor discrimination, odor identification, or odor detection threshold tasks (Bang et al., 2021). Since OD is a prodromal feature of PD, it was studied as an early diagnostic biomarker of the disease, which may help to identify patients for neuroprotective and disease-modifying clinical trials. However, as OD is not specific to PD, depending on olfaction tests only as a screening tool is not sufficient. Therefore, it is recommended to use other prodromal markers that may give a better positive predictive value (Fullard et al., 2017; De Rui et al., 2020). Regarding the treatment of OD, no effective pharmacological treatment was revealed, according to these two reviews (Armstrong and Okun, 2020; Seppi et al., 2019).

2.2. Constipation and Parkinson's Disease

Gastrointestinal (GI) dysfunctions are considered one of PD's most frequent non-motor autonomic symptoms (Metta et al., 2022a). They can affect any part of the GI tract and cause different disorders that progress with the period and severity of the disease, along with the stages of motor dysfunction (Camilleri, 2021). These disorders include sialorrhea, dysphagia, gastroparesis, defecatory dysfunction, fecal incontinence, and constipation. Although the mechanisms underlying the onset of GI symptoms are not fully understood, two major explanations have been proposed: misfolded α-synuclein protein aggregation, which forms LB, and autonomic neuron destruction (Chen et al., 2020).

Recently, constipation has been a significant area of interest in GI dysfunctions; it occurs in more than 80% of PD patients and is considered a prodromal feature of PD that might precede motor manifestations by several years (Metta et al., 2022a; Xu et al., 2022). Research has shown that males with less than one daily bowel movement were found to have 2.7 times greater odds of being diagnosed with PD compared to those who had a more regular frequency (Hustad and Aasly, 2020).

When pathological α-synuclein congregates in the structures that control the gut (the enteric nervous system [ENS] and the dorsal motor nucleus of the vagus nerve), abnormal gut motility and a faulty emptying process can occur. An imbalance in gut microbiota has been suggested to trigger α-synuclein accumulation. This leads to colonic movement and intestinal content issues, which result in constipation (Metta et al., 2022b; Xu et al., 2022). It is worth noting that the more Lewy neurites there are in the ENS, the more neuron loss occurs, exacerbating constipation (Xu et al., 2022). Similarly, there is an identical negative impact on stomach motility, which slows gastric emptying and results in nausea, bloating, and early satiety. In addition to constipation, these symptoms can lead to poor appetite and malnutrition (Breasail et al., 2021). After an 18-month follow-up of PD patients, one study showed that constipation was the most progressive symptom among the other GI symptoms, leading to poor quality of life (Camilleri, 2021). Several studies demonstrated that PD patients with RBD displayed a higher incidence and severity of constipation and, therefore, increased colonic volume and transit time compared to PD patients without RBD (Horsager *et al.,* 2022).

Constipation treatment in PD patients is generally similar to that in non-PD patients. The treatment involves changes in the nutritional pattern, such as consuming a high-fiber and water-rich diet. In addition, enemas and physical activity can produce some relief in constipation symptoms. Furthermore, bulk laxatives like psyllium and osmotic laxatives can help to soften feces and promote gut movement. Nonetheless, bulk laxatives should be used cautiously since adequate hydration is necessary. Other medications, such as chloride channel activators, serotonin agonists, levodopa, and probiotics, effectively improve constipation in PD patients (Chen et al., 2020; Palma and Kaufmann, 2018). Recent evidence suggests that squalamine appears to disassemble α-synuclein accumulation topically in the gut, which can alleviate constipation and reduce the central manifestations of PD (Camilleri, 2021). Fecal microbiota transplantation has also emerged as a novel method for treating PD, with promising results in improving both motor symptoms and constipation (Metta et al., 2022b).

2.3. REM Sleep Behavior Disorder and Parkinson's Disease

Sleep problems are among the most frequent non-motor features of PD (Almikhlafi, 2023; Mantovani et al., 2018; Matsumoto and Tsunematsu, 2021), affecting 40% to 90% of patients (Matsumoto and Tsunematsu, 2021). These disturbances develop during the prodromal stage of the disease, before the appearance of any observable motor or cognitive symptoms (Hu et al., 2023; Mantovani et al., 2018). Sleep issues negatively impact the patient's quality of life (Bohnen and Hu, 2019; Mantovani et al., 2018) and are one of PD's most upsetting non-motor symptoms (Bohnen and Hu, 2019).

The exact etiology of sleep symptoms in PD patients is unclear (Mantovani et al., 2018). The loss of neurons in sleep regulation

regions may lead to these alterations in normal sleep (Zuzuárregui and During, 2020).

These disturbances encompass a whole range of sleep problems (Stefani and Högl, 2020), including restless legs syndrome, circadian rhythm disturbances, insomnia, excessive daytime sleepiness, obstructive sleep apnea, and RBD. According to studies, 50% of PD patients suffer from RBD (Zuzuárregui and During, 2020).

RBD is the only sleep disturbance that has a clear link to the later development of PD (Gan-Or et al., 2018). It is a unique prodromal indicator of PD and other synuclein diseases (Mantovani et al., 2018; Shen et al., 2023). The median duration between the RBD onset and PD diagnosis is ten years, and this might provide the chance of an early diagnosis of PD (Zuzuárregui and During, 2020).

RBD is characterized by the absence of muscular atonia that typically occurs throughout REM sleep (Gan-Or et al., 2018; Gros and Videnovic, 2020). Therefore, RBD's features are recurrent sounds associated with sleep and\or complicated motor behaviors happening during REM sleep (Gros and Videnovic 2020), including numerous symptoms, from slight muscular spasms to severe complex movements. This may result in self-harm, bed partner harm, or falling out of bed (Zuzuárregui and During, 2020).

RBD makes the prognosis for PD worse; PD patients with RBD have more chance of suffering from dementia, autonomic problems, and severe motor symptoms and may need more doses of levodopa to manage the disease (Gan-Or et al., 2018; Gros and Videnovic, 2020).

However, in PD patients, the clinical motor symptoms do not appear until the loss of more than half of the dopaminergic neurons in the substania nigra pars compacta. At that point, the disease would be difficult to control. Therefore, early diagnosis is essential. It may be easier to control the disease if PD is discovered before observable symptoms emerge (Mantovani et al., 2018). This could be achieved by paying attention to sleep problems as an early common non-motor feature of PD (Matsumoto and Tsunematsu, 2021).

2.4. Depression and Parkinson's Disease

Depression is a common non-motor symptom of PD (Cong et al., 2022; Jellinger, 2022). It affects 40%—46% of PD patients, with a higher prevalence in men than women (Jellinger, 2022). Mood disorders are not often noticed because they overlap with motor and cognitive symptoms, so screening for depression is important for all PD patients (Ray and Agarwal, 2020). Several psychiatric manifestations have been noticed in PD patients, but depression is regarded as the most significant because of its impact on the lives of patients and their caregivers (Jellinger, 2022). There are many risk factors for depression in PD (DPD), such as genetic factors (depression is more common in PD patients having Gly2019ser mutation in the *LRRK2* gene. Patients having the *GBA* gene also have a higher probability of developing depression). The other risk factors are female gender, progressive levels of PD, association with cognitive impairment, and the onset of motor symptoms before the age of 40 (Lintel et al., 2021; Ray and Agarwal, 2020). Multiple studies showed that PD patients with poor sleep quality had higher levels and severity of depression than those who did not have sleep disorders (Ryan et al., 2019). Depressive symptoms may occur 20 years before motor symptoms or at any point to the advanced levels of the disease (Lintel et al., 2021; Ryan et al., 2019). The pathophysiology of DPD is still not clear enough. The first hypothesis is the dysregulation of monoamine neurotransmitters. The second is the degeneration of the serotonergic, dopaminergic, and noradrenergic pathways and nuclei. A recent study revealed the relationship between the alteration of hippocampal neurogenesis and DPD (Jellinger, 2022; Lim et al., 2018). It is known that 50%—80% of dopaminergic neurons are lost before motor symptoms begin, but the motor system has a compensatory way to postpone these symptoms. However, depression begins before motor symptoms. The early onset of depression may be related to the accumulation of α-synuclein in the brain. Some studies showed that the first place to accumulate this substance is the anterior olfactory nucleus, then the limbic system, then the substantia nigra, and finally the cortical regions, so that the loss of olfactory sense happens first followed by emotional disturbance, then the motor symptoms (Ryan et al., 2019).

Diagnosis of depression depends on many symptoms, such as depressive mood, loss of desire, weight fluctuations, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, loss of concentration, recurrent thinking of death, suicidal thoughts, and inappropriate guilt feelings. Note that there are several types of depression depending on the number and duration of symptoms (Ray and Agarwal, 2020). Numerous biomarkers elevate in depression-related PD, such as cytokines, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interferon-γ (IFN-γ) (Tizabi et al., 2019). High levels of interleukin-10 (IL-10), interleukin-6 (IL-6), TNFα, and soluble interleukin-2 receptor (sIL-2R) were discovered in blood samples (Prell et al., 2019). Changes in depressive PD patients' brains were thinning of cortical gray matter with atrophy of the hippocampus and thalamus (Ryan et al., 2019). Magnetic resonance imaging (MRI) found white matter loss, but more loss occurred in cases associated with cognitive and gait disorders (Jellinger, 2022). Functional MRI revealed increased functional conductivity in the limbic system but decreased conductivity between cortical and limbic systems (Ryan et al., 2019). Treatment of depression is divided into two parts: the pharmaceutical part and the non-pharmaceutical part. The first one is antidepressive drugs like selective serotonin reuptake inhibitors (SSRIs), which are considered the first line of treatment. Although tricyclic antidepressants are more effective than SSRIs, they have more side effects. There are also many other drugs to treat depression (Lim et al., 2018; Lintel et al., 2021). For non-pharmaceutical methods, electroconvulsive therapy (ECT) was found helpful for treating motor and non-motor symptoms without affecting cognitive function. It is also effective in treating pharmaco-resistant depression symptoms in PD patients (Takamiya et al., 2021). ECT was effective in 93% of cases; side effects were delirium and transient confusion (Ryan et al., 2019). A meta-analysis found that transcranial magnetic stimulation contributed to treating refractory depression, while other studies found no benefits from it (Lesenskyj et al., 2018; Ryan et al., 2019). Cognitive behavioral therapy was found to substantially decrease depression, in addition to physical exercise, which was found very helpful in improving depression symptoms and quality of life (Ryan et al., 2019).

Finally, DPD patients should be screened for metabolic disorders that mimic depressive symptoms before beginning treatment. We also should remember the effect of chronic diseases on the mentality and check for hypogonadism in men with refractory depression (Ray and Agarwal, 2020).

3. Conclusion

PD's prodromal symptoms, including hyposmia, constipation, sleep disturbances, and depression, may occur long before the motor manifestations and can be subtle and non-specific, making diagnosing the condition in its early stages difficult. Therefore, further investigations are necessary for those presenting with prodromal symptoms to facilitate an earlier diagnosis of PD. This would improve management outcomes and ultimately enhance patients' quality of life. This review highlights the role and importance of prodromal symptoms through PD development. However, more research is necessary to determine the time frame for symptoms' onset precisely

and adjust the diagnostic criteria of PD accordingly so that non-motor prodromal symptoms can also be considered.

Table of abbreviations:

CBT = cognitive behavioral therapy	OB = olfactory bulb
DPD = depression in Parkinson's disease	OD = olfactory dysfunction.
GI = gastrointestinal	PD = Parkinson's disease
IFN-γ = interferon-γ	RBD = REM sleep behavior disorder
IL-1β = interleukin-1β	REM = rapid eye movement.
IL-6 = interleukin-6	SSRIs = serotonin reuptake inhibitors
IL-10 = interleukin-10	sIL-2R = soluble interleukin-2 receptor
LB = Lewy body	TNF-α = tumor necrosis factor-α
MRI = magnetic resonance imaging	

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