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REVIEW

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A look back at the prodromal findings in Parkinson's disease

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Abstract

Background Parkinson's disorder is a neurodegenerative illness that displays motor and non-motor manifestations. There is no definite cause of Parkinson's disorder, nor is there a medicine or treatment to prevent it.

Main body of the abstract Non-motor manifestations of the disorder are referred to be progressive symptoms of the disorder by medical specialists since they might emerge chronically several years before motor symptoms. Among these symptoms are a loss of smell, constipation, a sleep disorder, melancholy, sexual dysfunction, and depression. In this paper, we focus on several different aspects related to Parkinson's disorder (PD) prodromal features and their prevalence in PD patients, pathophysiology, treatment (if possible), and the impact of prodromal symptoms on diagnosis, prognosis of life of patients.

Short conclusion All people who present with these non motor prodermal symptoms should be considered by specialists for further tests for early diagnosis of this disease.

Keywords Parkinson, Hyposmia, Constipation, Sleep disturbances, Depression

Backgroud

Parkinson's disorder is the prevalent type of neurological movement illness, affecting 2% to 3% of persons over the age of 65 (Kouli et al. 2018; Poewe et al. 2017). In the majority of instances, the exact cause of PD has yet to be completely understood. There are various clinical features of the disease, such as degeneracy of dopaminergic neurons in the substantia nigra pars compacta(SNpc) and Lewy body (LB) pathology (intracellular inclusions of an abnormal protein termed synuclein) (Cabral-Pacheco et al. 2020; Hayakawa et al. 2012). In terms of its clinical presentation, PD is a degenerative disease that can manifest itself in either motor or non-motor ways (DeMaagd and Philip 2015). Even though non-motor symptoms often present several years earlier than motor dysfunction, PD is nonetheless diagnosed based on motor manifestations such as bradykinesia, stiffness, and tremor (Lee and Koh 2015). Non-motor symptoms have recently received a lot of attention in identifying people in the prodromal stage of Parkinson's disorder (Taguchi et al. 2020). Olfactory dysfunction (OD), constipation, Rapid eye movement(REM), Rapid eye movement behavior disorder (RBD), and sadness are the most prominent prodromal symptoms (Solla et al. 2023). The quality of life of the patient is influenced more by the current symptoms than by the normal motor symptoms (Bock et al. 2022). In addition to this, they are vital indicators that are capable of predicting the clinical manifestation of the disease. In addition, the prodromal non-motor manifestation of Parkinson's disorder could be beneficial in the early diagnosis, which in turn could provide better care and a better prognosis (Fullard et al. 2017a). This manuscript addresses the prodromal symptoms of Parkinson's disorder and the value of these manifestations in the early stages of the condition.

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Main text

Constipation

According to studies, gastrointestinal (GI) tract dysfunction is one of the prevalent non-motor autonomic manifestation of Parkinson's disorder (Han et al. 2022). Sialorrhea, dysphagia, gastroparesis, defecatory dysfunction, fecal incontinence, and constipation are some of the conditions that fall under this category. However, the mechanisms of gastrointestinal symptoms are not completely known; two basic hypotheses exist: misfolded and aggregated synuclein protein and autonomic neuronal death (Kim and Sung 2015).

Constipation is a prodromal and common symptom of Parkinson's disorder (Metta et al. 2022a), and it has recently become a prominent focus of research in the field of GI dysfunctions. When aberrant synuclein aggregates in the tissues that control the gut (enteric nervous system(ENS) and the dorsal nucleus of the vagus nerve), which can lead to irregular gut motility as well as a malfunction in the emptying process. It was postulated that an imbalance in the microbiota of the gut could be the cause of a buildup of alpha-synuclein. As a result, it affects the movement of the colon and the contents of the intestinal tract, leading to constipation (Rui et al. 2020; Xu et al. 2022; Metta et al. 2022b). It is important to remember that the more Lewy neurites present in the ENS, the higher the rate of neuron death, which in turn makes constipation even worse (Xu et al. 2022). In the same manner, there is an identical detrimental impact on the stomach's motility, which slows the rate at which the stomach empties, which in turn causes nausea, bloating, and early gas. These manifestations, in addition to causing constipation, might lead to a loss of appetite and, consequently, malnutrition (By-nc-nd et al. 2021). Constipation was the most progressive symptom among the other GI symptoms, leading to poor quality of life, according to one study that followed PD patients for 18 months and found that the condition led to a decline in overall health (Camilleri 2021). Patients with Parkinson's disease who took additional drugs, such as chloride channel activators, serotonin agonists, levodopa, and probiotics, experienced a significant reduction in their symptoms of constipation (Xu et al. 2022; Horsager et al. 2022). According to recent data, Squalamine (a steroid-polyamine with antimicrobial activity) appears to deconstruct beta-synuclein buildup topically in the gut. This can improve constipation and diminish the cerebral symptoms of Parkinson's disorder (Xu et al. 2022; Metta et al. 2022b; Camilleri 2021; Horsager et al. 2022).

Depression

Depression is a prevalent non-motor manifestation of Parkinson's disorder (Marinus et al. 2018). It affects 40–46% of patients, and males are more commonly affected than females (Jellinger 2022). As mood disorders commonly overlap with motor and cognitive symptoms, screening for depression is essential for all patients with Parkinson's (Torbey et al. 2015). There are several risk factors for depression in Parkinson's disorder, including genetic factors. Patients who carry the GBA gene are also more susceptible to depression. Female gender, increasing degrees of PD, correlation with cognitive impairment, and onset of motor symptoms before age 40 are other risk factors (Ray and Agarwal 2020; Lintel et al. 2021). Many research have shown that Parkinson's patients with needy sleep quality have higher levels and intensity of depression than people without sleep disorders, and symptoms of depression can appear 20 years before motor symptoms or at any stage of the disease (Lintel et al. 2021; Ryan et al. 2019). The pathophysiology of depression Parkinson's disease(DPD) is currently unclear. The first hypothesis is that monoamine neurotransmitters are dysregulated. The second is the serotonergic, dopaminergic, noradrenergic pathways and nuclear destruction. According to Politis et al. (2012), The emergence of non-motor manifestation in patients could be linked to serotonergic neuron loss. 5-HT and its metabolite, 5-HIAA, are found at lower concentrations in the CSF of depressed people.

Recent research has shown a link between changes in hippocampal neurogenesis and DPD (Ryan et al. 2019). It is known that 50–80% of dopaminergic neurons are lost before motor symptoms appear, but the motor system has a compensatory mechanism to delay these symptoms. On the other hand, depression precedes motor symptoms. The agglomeration of synuclein in the brain is also related to the early onset of depression, and the first place of accumulation of this substance is the anterior olfactory nucleus, followed by the limbic system, then the substantia nigra, and finally, the cerebral cortex. Loss of smell occurs first, followed by emotional disturbance, and then motor symptoms (Ryan et al. 2019; Politis et al. 2012; Raison et al. 2006).

Evidence suggests that chronic immunological activation and/or chronic inflammation are pathophysiological mechanisms associated with depression in Parkinson's disorder. It is widely recognized that the creation of Lewy cells and the loss of dopaminergic neurons activate microglia, which create neurotoxic substances and increase the production of cyclooxygenase (COX), resulting in a rise in prostaglandin (PG) synthesis (Prell et al. 2019; Gros and Videnovic 2020). Inflammatory cytokines are elevated in these patients' SNpc, striatum, and CSF. In their research, Tino Pearl and colleagues reported an increase in the inflammatory process in the brain and peripheral blood of Parkinson's patients. Blood samples

contained high levels of interleukin-10, IL-6, TNF, and soluble interleukin-2 receptor (sIL-2R) (Zarkali et al. 2022). Proinflammatory cytokines and PGE2 may decrease 5-HT levels by activating indoleamine 2,3-dioxygenase (IDO), an enzyme that converts tryptophan into tryptophan catabolites(TRYCATs) and nicotinamide (Fig. 1).

Treatment of depression is divided into two parts: drug and non-drug. The first line of drug treatment is selective serotonin reuptake inhibitors (SSRIs) (Moraczewski et al. 2022). Electroconvulsive therapy (ECT) is effective for treating motor and non-motor manifestations as well as drug-resistant depression (Takamiya et al. 2021; Borisovskaya et al. 2016). A meta-analysis found that transcranial magnetic stimulation helped treat refractory depression, although other studies reported little benefit (Ahadiat and Hosseinian 2023). Cognitive behavioral therapy (CBT) and physical training have been shown to reduce depression symptoms significantly (Takamiya et al. 2021).

Genetic abnormalities

As well as advancements in molecular genetics, evidence from family and twin studies and other researchers, has revealed that hereditary factors play an essential role in the development of Parkinson's disorder. Asymptomatic carriers of mutations that cause monogenic forms of the illness can provide the clearest details about the evolution of prodromal features (Struhal et al. 2014; Ahadiat and Hosseinian 2023).

The most frequent monogenic cause of Parkinson's disorder is a mutation in the autosomal dominant Leucine Rich Repeat Kinase-2(LRRK2) gene. LRRK2 has diverse roles in neuronal cell death or neuroinflammation in astrocytes and microglia. Recently, the inhibitor of this gene has become the most advanced drug in the treatment of Parkinson's disorder (Iseki et al. 2023).

The G2019S mutation in the LRRK2 gene is the most frequent pathogenic mutation found in Parkinson's disorder patients worldwide. This mutation is responsible for up to 1–6% of sporadic and 3–19% of familial Parkinson's disorder, with a greater prevalence in Ashkenazi Jews (Tolosa et al. 2020; Sidransky et al. 2009; Ahadiat and Hosseinian 2023).

There is currently no reliable approach for determining who is prone to the condition. The identification and subsequent monitoring of people who carry the LRRK2-G2019S mutation but who have not yet acquired

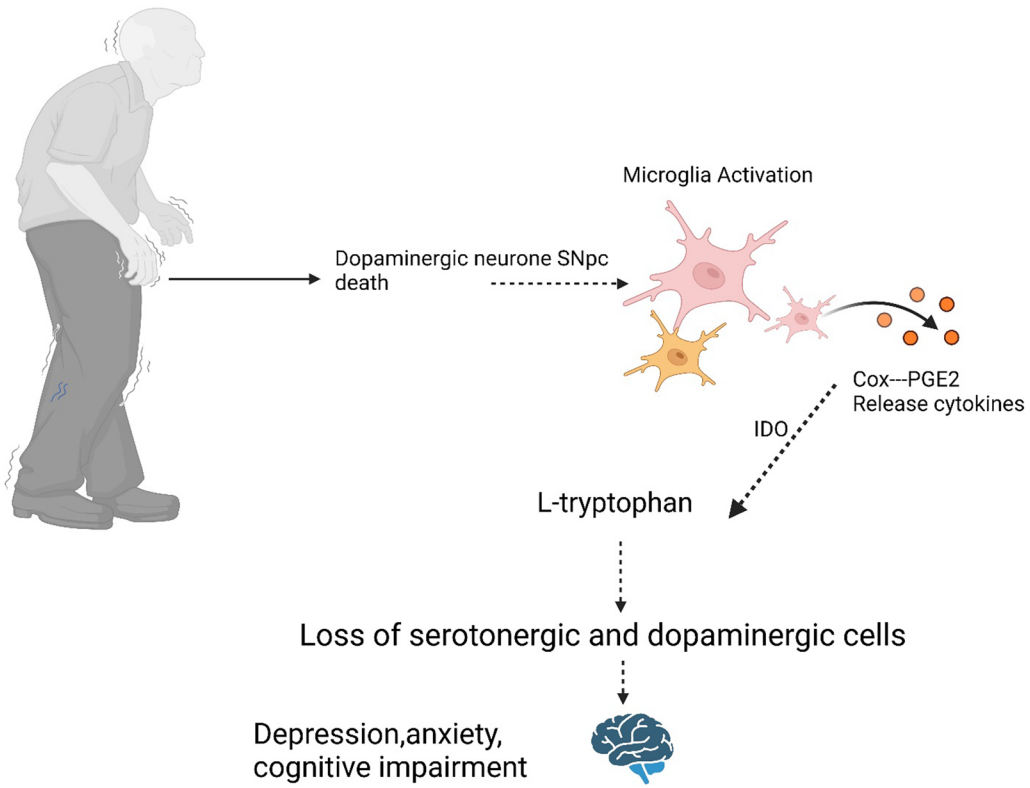

Fig. 1 Scheme proposed for the cause of depression in Parkinson's disease. SNpc: substantia nigra compact part COX: cyclooxygenase; PGE2: prostaglandin E2; IDO; 5-HT

the motor manifestations of Parkinson's disorder gives a one-of-a-kind opportunity for researching the pre-symptomatic stage of the disease (Tolosa et al. 2020). GBA (glucocerebrosidase) mutations and LRRK2 variations are the most frequent genetic risk factors for late-onset Parkinson's disorder. There are mutations in the GBA1 gene in approximately 5–10% of people who have Parkinson's disorder (PD), and having a GBA mutation can increase the chance ratio for PD in its carriers by roughly sevenfold (Hustad and Aasly 2020a; Ahadiat and Hosseinian 2022).

Sleep disorder

One of the most prevalent non-motor manifestations of Parkinson's disorder, sleep issues impact 40–90% of patients (Videnovic and Golombek 2013). This symptom is in the prodromal stage, which can be one of the most painful symptoms of this disease, which affects the quality of life (Baumann-Vogel et al. 2020).

The exact cause of this is unknown. Neuronal loss in sleep regulatory regions may be responsible for these changes in normal sleep. Restless legs syndrome (RLS), circadian rhythm abnormalities, insomnia, excessive daytime sleepiness (EDS), obstructive sleep apnea(OSA), and RBD are examples of these problems. According to studies, RBD affects 50% of individuals with Parkinson's disorder (Rafael et al. 2020). RBD is the only sleep condition linked to Parkinson's disorder progression (Sixel-Döring et al. 2016). According to a meta-analysis (Zhang et al. 2020), the outbreak of RBD in Parkinson's disorder is roughly 42.3%. Furthermore, over 70% of PD patients with RBD also had dementia. The glymphatic system is a waste removal system CNS (https://en.wikipedia.org/wiki/Glymphatic_system).

As the glymphatic system's function gradually degrades with age, brain health becomes increasingly exposed to pathological damage from toxic proteins. As a result, more evidence suggests a relationship between Alzheimer's disease and glymphatic dysfunction, which many studies currently point to Kress et al. (2014) and Peng et al. 2016).

According to current research, there is a bidirectional association between sleep disruption and dopaminergic neurodestraction. Many pathogenic mechanisms are at work, including alpha-synuclein buildup, neuroinflammation, and glymphatic system disruption. Sleep deprivation contributes significantly to glymphatic dysfunction, reducing alpha-synuclein clearance. As a result, alpha-synuclein accumulation is linked to recurrent sleep disturbances, and alpha-synuclein also promotes neuroinflammation and AQP4 insufficiency, which maintains glymphatic dysfunction and leads to dopaminergic degradation in the SN and other brain regions (Massey et al. 2022) (Fig. 2).

The average interval between the onset of RBD and the detection of Parkinson's disorder is ten years, suggesting that early detection of PD may be possible (Lim et al. 2018). RBD is distinguished by the absence of muscle atony, which is common during REM sleep (Zhang et al. 2008; Boeve 2010). Consequently, symptoms of RBD include repetitive sleep-related sounds and/or complex motor activity that occurs during REM sleep, which

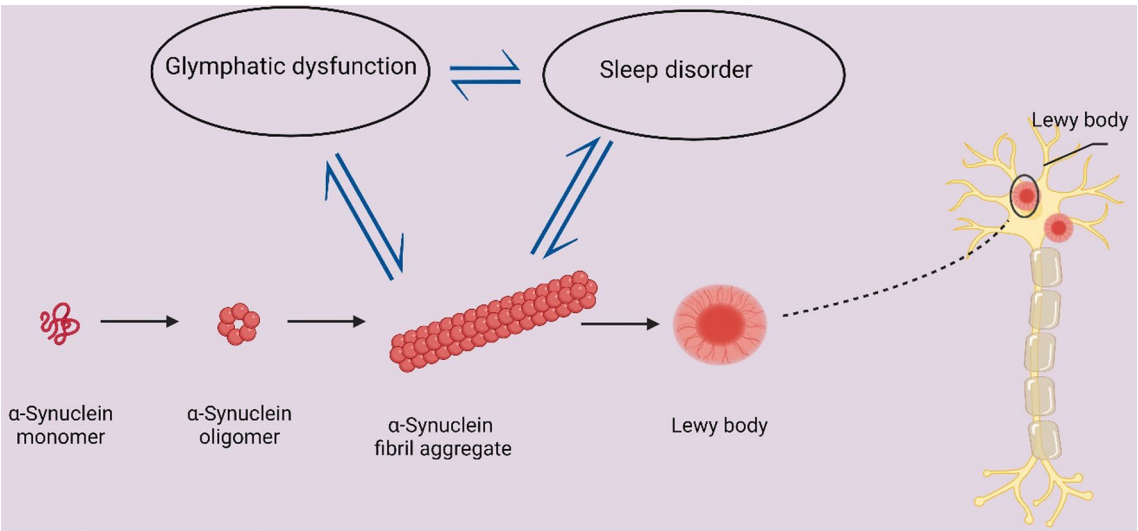

Fig. 2 The disruption of one's sleep has been identified as both a risk factor and a chronic symptom of Parkinson's disorder (PD). A malfunction in the Glymphatic system may contribute to Parkinson's disorder by permitting an agglomeration of alpha-synuclein and other solutes outside of cells

includes a range of symptoms from minor muscle spasms to severe complex movements (Bollu and Sahota 2017; Barasa et al. 2021). RBD worsens the prognosis of Parkinson's disorder. RBD patients suffer more from dementia, autonomic problems, and severe motor symptoms and may require higher doses of levodopa for treatment (Hustad and Aasly 2020b; Gupta and Shukla 2021). However, until more than 50% of the dopaminergic neurons in the substantia nigra are lost, motor manifestation of Parkinson's disorder do not appear. Therefore, early detection is very vital (Leonhardt et al. 2019; Brown et al. 1990).

Erectile dysfunction

ED is a typical symptom of Parkinson's disorder, although it is generally underreported. Patients with PD might experience it at any stage of the disease, and this problem affects both men and women (Malek et al. 2016; Pfeiffer 2012; Coon et al. 2018). Although the particular etiology of ED is not extensively understood (Palma and Kaufmann 2018; Perez-Lloret. 2021), it is generally accepted as a component of a wider range of autonomic disorders present in PD.

In summary, the loss of dopaminergic neurons can increase serum prolactin, which blocks the release of GnRH and hence lowers the synthesis of luteinizing hormone (LH) and testosterone; however, many men with PD do not experience this effect. Some clinicians wrongly believe that low testosterone in patients is age-related, even though it may be identified beyond the fourth decade of life (Fig. 3).

A meta-analysis comparing serum prolactin levels in patients with PD to healthy controls did not show a significant difference. Also, a clinicopathological investigation discovered that premature onset of autonomic dysfunction, including Erectile dysfunction**,** was related to earlier disease progression and shorter survival in Parkinson's patients. These findings show that Erectile dysfunction may be a particularly prodromal feature of Parkinson's disease. A few clinical trials for the therapy of ED in PD are currently being conducted. PDE5-I medications, in particular sildenafil, give the impression of being both effective and safe, but the evidence we currently have about testosterone treatment is ambiguous (Malek et al. 2016; Pfeiffer 2012; Coon et al. 2018; Palma and Kaufmann 2018).

Hyposmia and Parkinson's disease

Olfactory Dysfunction (OD), or hyposmia, is one of the first and most apparent non-motor manifestations of Parkinson's disorder, affecting 50%–90% of patients (Perez-Lloret. 2021; Liu et al. 2021). It usually emerges in the early stages of Parkinson's disorder, up to 4 years

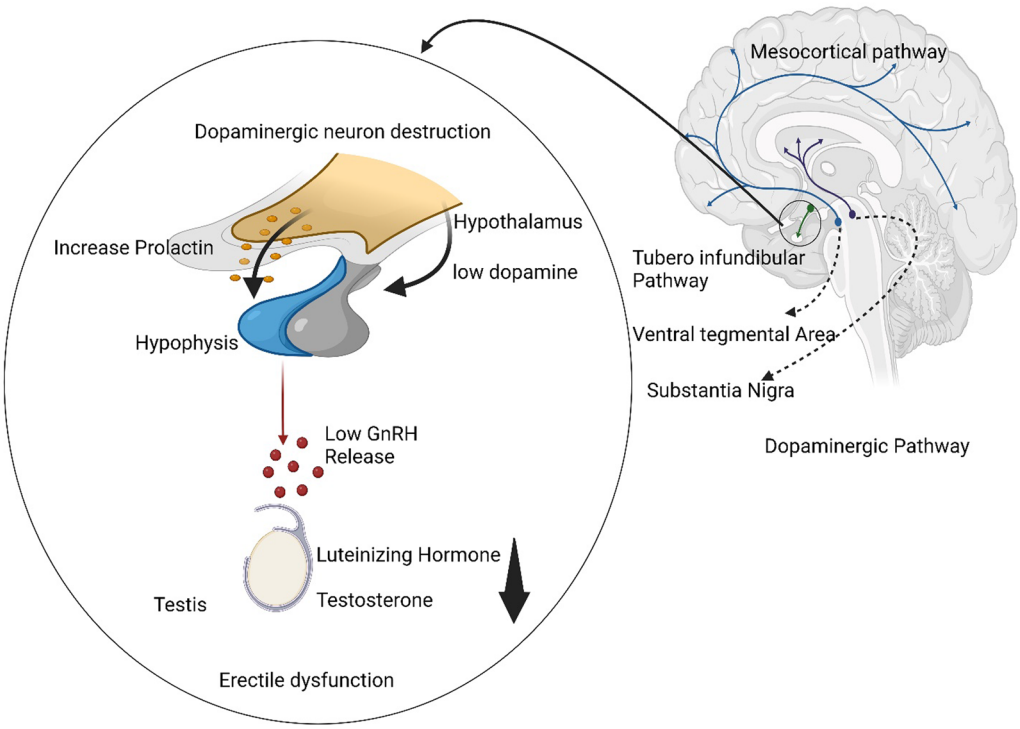

Fig. 3 Dopaminergic pathways (Tubero infundibular Pathway) and hypothalamic-pituitary–gonadal axis in Parkinson's disorder. Abnormalities in each part of the axis could indicate a novel path for studies on medication intervention in men's libido

before the start of hallmark motor features (Deebel et al. 2022). The pathophysiology of Parkinson's illness-related OD is not entirely known. However, the LB pathology is thought to be the main culprit, with aberrant deposits of -synuclein in the neurons of the olfactory bulb (OB) causing neurodegeneration (Duc Nguyen et al. 2022). Braak's hypothesis attempted to explain the early onset of OD preceding motor symptoms by positing that a pathogen enters the nasal cavity and affects the neurons of the OB, causing synuclein pathology, which then spreads through the olfactory tract toward the central nervous system, eventually reaching the Dopaminergic neurons located in the SNpc and causing motor dysfunction. Although multiple studies support this notion, not all Parkinson's patients exhibit the same pattern (Liu et al. 2020). Environmental toxins (pesticides, air pollution, and metals) have been proposed as probable preventive factors that may trigger the pathology using a similar mechanism. OD is also characterized by dysregulation of neurotransmitters, including dopamine, serotonin, and acetylcholine (Rui et al. 2020). Dopamine deficiency is strongly linked to the classic motor symptoms of Parkinson's illness; however, the dopamine mechanism of action in OB is distinct and poorly understood. In a research project, the authors evaluated the neuroprotective effects of dopamine D2 receptor agonists on neurotoxicity caused by the AMPA receptor (neuronal effects of glutamate) in olfactory bulb patients who had olfactory dysfunction (OD) (Fullard et al. 2017a).

Quinpirole has been shown to increase D2R expression and significantly reduce glial cell activation (by D2R/Akt/GSK3- signaling pathways). Moreover, olfactory synaptic inflammation induced by AMPA receptor-induced neurotoxicity improves olfactory function in mice. The level of Ca2+ can be controlled by a molecular switch called GRIA2. It is known that the surface expression of AMPA receptor GluR1 increases in the olfactory bulb of OD rats, whereas the surface expression of GRIA2 decreases in these rats, but injection of quinine pyrrole has the effect of reversing the result and improving the nerve damage to the olfactory bulb (Fullard et al. 2016). Pathophysiology 75% of patients with PD-related hyposmia do not appear to have previously been aware of their olfactory impairment (Bang et al. 2021).

Olfactory function is also linked to other non-motor symptoms of the disorder and may predict cognitive deterioration. Nevertheless, due to the fact that OD is not unique to Parkinson's disease, relying just on olfaction tests as a screening tool is insufficient. As a result, other prodromal markers with a better positive predictive value have been proposed (Fullard et al. 2017b). According to the findings of these two investigations, no known pharmaceutical treatment is currently succeeding in OD.

Conclusions

Hyposmia, constipation, sadness**,** erectile dysfunction, and sleep problems are all prodromal signs of Parkinson's disease. These symptoms may appear long before the motor manifestations and can be subtle and non-specific, making early diagnosis challenging. As a result, further tests are required for patients presenting with prodromal symptoms to facilitate an earlier diagnosis of Parkinson's disease. This would improve management outcomes and, as a result, the overall quality of life. More research is needed, however, to precisely define the period for the development of symptoms and alter the PD diagnostic criteria accordingly so that non-motor prodromal symptoms are also addressed.

Abbreviations

CBT	Cognitive behavioral therapy
ECT	Electroconvulsive therapy
EDS	Excessive daytime sleepiness
ENS	Enteric nervous system
GI	Gastrointestinal
LB	Lewy body
DPD	Depression Parkinson's disease
OB	Olfactory bulb
OD	Olfactory dysfunction
OSA	Obstructive sleep apnea
PD	Parkinson's disease
RBD	Rapid eye movement behavior disorder
REM	Rapid eye movement
RLS	Restless legs syndrome
SSRIs	Serotonin reuptake inhibitors
sIL-2R	Soluble interleukin-2 receptor
sNPc	Substantia nigra pars compacta
IDO	Indoleamine 2,3-dioxygenase
TRYCATs	Tryptophan catabolites
LRRK2	Leucine Rich Repeat Kinase-2
LH	Luteinizing hormone

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All authors have read and approved the manuscript. SAAA and ZH approved the manuscript topic, both initiated the search and began writing the initial manuscript, and together edited and drafted the final manuscript.

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Ethics approval and consent to participate

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Competing interests

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