Premotor and nonmotor features of Parkinson's disease

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Purpose of review

This review highlights recent advances in premotor and nonmotor features in Parkinson's disease, focusing on these issues in the context of prodromal and early-stage Parkinson's disease.

Recent findings

Although Parkinson's disease patients experience a wide range of nonmotor symptoms throughout the disease course, studies demonstrate that nonmotor features are not solely a late manifestation. Indeed, disturbances of smell, sleep, mood, and gastrointestinal function may herald Parkinson's disease or related synucleinopathies and precede these neurodegenerative conditions by 5 or more years. In addition, other nonmotor symptoms such as cognitive impairment are now recognized in incident or de-novo Parkinson's disease cohorts. Many of these nonmotor features reflect disturbances in nondopaminergic systems and early involvement of peripheral and central nervous systems, including olfactory, enteric, and brainstem neurons as in Braak's proposed pathological staging of Parkinson's disease. Current research focuses on identifying potential biomarkers that may detect persons at risk for Parkinson's disease and permit early intervention with neuroprotective or disease-modifying therapeutics.

Summary

Recent studies provide new insights into the frequency, pathophysiology, and importance of nonmotor features in Parkinson's disease as well as the recognition that these nonmotor symptoms occur in premotor, early, and later phases of Parkinson's disease.

Keywords

autonomic, behavioral, cognitive, gastrointestinal, mood, sleep

INTRODUCTION

Parkinson's disease is now recognized as a multisystem disorder with motor and nonmotor features. The frequent and diverse clinical nature of these symptoms reflects the widespread neurochemical and neuroanatomical changes that occur throughout the course of Parkinson's disease, with involvement of not only the dopaminergic nigrostriatal system, but also serotonergic and noradrenergic brainstem areas, cholinergic frontal and brainstem regions, among others. From observational and longitudinal studies, several nonmotor features affecting smell, mood, sleep, and autonomic function have now been linked to the later development of Parkinson's disease and neurodegenerative diseases. Furthermore, other nonmotor symptoms such as cognitive impairment, autonomic dysfunction, and sleepiness have been identified early in de-novo, untreated Parkinson's disease patients. As such, recognition of these nonmotor symptoms, especially in the context of prodromal and early Parkinson's disease, has led to critical thinking (or rethinking) regarding how we define Parkinson's disease, how we can best identify populations of people at risk either for developing the disease or its later complications and utilize biomarkers, and how or when we might be able to intervene with neuroprotective or disease-modifying therapies [1▪,2▪▪]. This review will discuss recent advances in premotor and nonmotor features in Parkinson's disease, focusing on these issues in the context of prodromal and early-stage Parkinson's disease.

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KEY POINTS

- Decreased sense of smell, depression, night-time sleep disturbances, mood, and gastrointestinal problems symptoms are recognized as part of a premotor phase of Parkinson's disease, manifesting years before the classic motor symptoms.
- Along with a variety of biomarker techniques, premotor symptoms have the potential to serve as early diagnostic markers of Parkinson's disease and ultimately, an intervention point for neuroprotective or disease-modifying strategies.
- Nonmotor features accompany all stages of Parkinson's disease, from prodromal to early and advanced disease, frequently reflect underlying nondopaminergic mechanisms, and substantially impact patients' quality of life.

PREMOTOR SYMPTOMS AS A PRODROME TO PARKINSON'S DISEASE

Several nonmotor symptoms are noted to precede the cardinal motor features of Parkinson's disease, and thus have been termed 'premotor'. These nonmotor symptoms may reflect the earliest pathological changes in the nervous system that are associated with Parkinson's disease. This section highlights several premotor features most suggestive of later development of Parkinson's disease, including sleep dysfunction, impaired olfaction, constipation, and mood changes.

Rapid eye movement sleep behavior disorder

Of all clinical markers, rapid eye movement sleep behavior disorder (RBD) is, by far, associated with the highest Parkinson's disease risk. The original description of RBD as a prodromal marker reported that 38% developed Parkinson's disease after an average 5-year follow-up. On continued follow-up, 81% of these patients eventually developed neurodegenerative disease [3]. Similarly, the Barcelona cohort reported a 45% risk of neurodegeneration at 5 years of follow-up [a rate that also includes mild cognitive impairment (MCI) as a disease outcome]; this number has risen to 76% at 14-year follow-up [4▪]. The Montreal cohort reported that 40% of RBD patients developed a neurodegenerative synucleinopathy at 10-year follow-up [5]. Additional follow-up of this cohort with annual examinations is observing higher risks of neurodegeneration, with recent estimates of over 50% at 7 years (unpublished data). Slightly lower risks (i.e., 38% at 9-year follow-up) were reported from a Hong Kong cohort [6]; the lower figure may be related to the selection of patients without motor signs, and a high rate of antidepressant use as antidepressant-triggered RBD has been associated with a lower risk of Parkinson's disease [7]. Finally, having a clinical history suggestive of dream-enactment behavior has been associated with increased risk of MCI and dementia in a population-based study [8]. Most cohorts find that patients with idiopathic RBD are at approximately equal risk for both Parkinson's disease and dementia with Lewy bodies (DLB), two synucleinopathies with considerable clinical overlap.

This very high conversion rate with idiopathic RBD has extremely important implications for future neuroprotective therapy; these risks may be high enough to consider idiopathic RBD patients as eligible for neuroprotective therapy against Parkinson's disease and DLB (when it becomes available). Moreover, RBD patients represent ideal candidates for neuroprotective trials as one can intervene relatively early in the disease process, and before symptomatic treatment of parkinsonism or dementia confounds the outcome assessment. Finally, RBD patients can provide a 'test lab' for other potential predictors of disease: prospective studies in these patients have suggested that markers such as dopaminergic functional imaging [9], transcranial ultrasound [9], whole-brain glucose utilization single-photon emission computed tomography [10], olfaction [11], decreased color vision [11], and subtle motor dysfunction [12] can serve as prodromal markers of Parkinson's disease or DLB.

Olfaction

Up to 85% of patients with Parkinson's disease have olfactory loss, and this is measurable very early in disease. The population-based Honolulu-Asia Aging study assessed olfactory function in Japanese-American men, using a 12-item cross-cultural smell identification test [13]. Those in the lowest quartile had a 5.2-fold increased risk of developing Parkinson's disease. Moreover, those in the lowest tertile of olfaction function had 11-fold odds of having incidental Lewy bodies on autopsy, even without established Parkinson's disease [14]. A Dutch study examined family members of Parkinson's disease patients and found that those with hyposmia had greater dopaminergic denervation on functional neuroimaging. Moreover, four out of 40 patients within the lowest decile of olfactory function developed Parkinson's disease over the next 2 years, compared with zero out of 360 with preserved olfaction [15]. In the Prospective Validation of Risk factors for the development of Parkinson Syndromes study, a prospective population-based follow-up of 1850 subjects, impaired olfaction was associated with a 3.94

odds ratio (OR) of developing Parkinson's disease [16]. In the Parkinson-Associated Risk Study, olfactory loss has been associated with other potential markers of prodromal Parkinson's disease, including constipation, anxiety, depression, and dream-enactment behavior (i.e., probable RBD) and mild motor symptoms (prospective findings have not yet been published) [17▪]. Finally, in RBD patients, the presence of olfactory loss was associated with a three-fold increased risk of developing Parkinson's disease or DLB in a 5-year prospective study [11].

Similar to many markers, there are some limitations to olfactory testing. First, the diagnostic lead time gained by its testing is unclear. In the Honolulu-Asia Aging study, the predictive value of the marker was only present in the first 4 years of follow-up. Similarly, the Dutch cohort found that only one additional patient with hyposmia developed Parkinson's disease in the second 3-year follow-up [18]. This may suggest that olfactory loss becomes apparent only 2–5 years before motor Parkinson's disease. However, studies in RBD populations have found clear olfactory loss up to 8 years before disease development, suggesting that subpopulations may have longer lead times. Second, the specificity of olfactory loss to developing Parkinson's disease is low. To illustrate, all of the patients in the lowest olfactory quartile of the Honolulu-Asia Aging study had anosmia, but only 10 out of 549 developed the disease [13].

Constipation

There is increasing evidence that constipation can identify prodromal Parkinson's disease. In manifest Parkinson's disease, colon biopsies show neuronal synuclein deposition in 60–70% of cases. This generally occurs in a rostral-caudal gradient, with only a minority of lower colon or rectal biopsies positive [19,20]. In the Honolulu-Asia Aging study, 24% of patients with constipation (defined as bowel movement frequency <1 per day) had incidental Lewy bodies (iLBD) on autopsy, compared with an iLBD prevalence of 12% in the study population [21]. A recent study described deposition of colonic synuclein in three Parkinson's disease patients from the colonoscopy samples taken 2–5 years before diagnosis of clinical Parkinson's disease [22▪]. However, sensitivity and specificity remain unclear; in an autopsy study, Beach *et al.* [20] described gastrointestinal synuclein deposition in only 20% of patients with iLBD, suggesting that sensitivity may be low.

Clinically, there is also prospective evidence that constipation can precede Parkinson's disease. Consistent with their findings in iLBD, the Honolulu-Asia Aging study found that men with bowel movement frequencies less than one per day were at two to five-fold increased risk of developing Parkinson's disease in the future. Savica *et al.* [23] found that constipation, as documented in medical records, was associated with a 2.5-fold increased odds of Parkinson's disease. Finally, Gao *et al.* [24] found that bowel movement frequency less than three per week was associated with a five-fold increased risk of Parkinson's disease in men and a 2.2-fold increase in women. Of interest, both the Honolulu and Savica studies found constipation greater than 15 years before Parkinson's disease diagnosis, suggesting that constipation is either a very early marker or even a risk factor (by contrast, Gao found that the risk was only elevated in the first 6 years of follow-up). As with olfaction, a major difficulty with the constipation is specificity – constipation occurs in up to 25% of the general population, ensuring a low positive predictive value.

Mood

Depression and anxiety are relatively common features of Parkinson's disease, occurring in approximately 30% of cases, often early in disease. Studies examining depression and anxiety as prodromal features show relatively modest, but consistent, links. In a nested case-control study in the Netherlands, patients at time of Parkinson's disease diagnosis had a 2.4-fold increased prevalence of depression diagnosis [25]. A database study of general practitioners found that prescription of antidepressants was associated with diagnosis of Parkinson's disease; however, this relationship was strongest for the first 2 years, suggesting a relatively short prodromal interval [26]. Fang *et al.* [27], analyzing data from the National Institute of Healthy-American Association of Retired Persons Diet and Health Study follow-up survey, found that patients diagnosed with Parkinson's disease had a 2.7-fold OR of depression in the 1–5 years preceding diagnosis. This relationship was also present even at intervals of greater than 15 years before Parkinson's disease diagnosis ($OR = 1.8$). Anxiety and depression are closely linked in Parkinson's disease, suggesting that anxiety may also be a risk factor. One analysis from the Health Professionals cohort found that phobic anxiety was associated with a 1.5-fold increased risk of Parkinson's disease, and prescription of medications for anxiety had a 1.6-fold increase [28]. Also, high anxiety scores on the Minnesota Multiphasic Personality Inventory were associated with an OR of 1.6 for the development of Parkinson's disease, a relationship that was present for very long prodromal intervals [29]. Related to anxiety, there is some evidence of a Parkinson's disease personality, characterized by lower novelty seeking and higher harm avoidance on personality scales (these are features also seen in anxious patients) [30,31]. Although this may be a prodromal feature, it may also be a risk marker because studies have described differences even in young adulthood.

NONMOTOR FEATURES IN EARLY PARKINSON'S DISEASE

Although the number and severity of nonmotor symptoms increase with advancing Parkinson's disease, they occur at all stages of Parkinson's disease, including prodromal symptoms (discussed above) and at the time of diagnosis when motor symptoms are already present. Nonmotor symptoms in Parkinson's disease are diverse in their presentation and timing, with some such as dementia and psychosis more likely occurring in later disease stages, and others such as sleep and autonomic disturbances distributed throughout early and later stages. In recent years, there has been increased recognition of the frequency of nonmotor symptoms, their impact on patients and caregivers, and the need for improved therapeutics. Several studies include incident Parkinson's disease cohorts, and in some cases, patients not yet treated with dopaminergic medications (i.e., de-novo, untreated, or drug-naïve) or those with short disease durations. Efforts to study large de-novo cohorts with longitudinal follow-up are ongoing worldwide [i.e., Parkinson's Progression Marker Initiative; ParkWest in Norway, Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation-Parkinson's Disease (ICICLE-PD) in the United Kingdom, Cambridgeshire Parkinson's Incidence from GP to Neurologist (CamPaiGN) in the United Kingdom, and De Novo Parkinson in Germany, among others] and several of these studies are discussed in this review. In a large retrospective review of pathologically confirmed cases, nonmotor features were the presenting complaint in about 20% of Parkinson's disease and were an important source of misdiagnosis or delayed diagnosis [32].

Assessment of nonmotor symptoms

Frequency estimates have been ascertained in several large cohorts of de-novo or early Parkinson's disease patients using a variety of comprehensive scales for the assessment of nonmotor symptoms. These include the nonmotor symptom questionnaire (NMSQuest) [33], nonmotor symptoms scale (NMSS) [34], Movement Disorder Society-revised Unified Parkinson's Disease Rating Scale [35], and individual rating scales for specific nonmotor domains (e.g., daytime sleepiness, night-time sleep, cognitive impairment, autonomic function). The NMSQuest is a 30-item screening tool designed to capture the presence of nonmotor symptoms over the past month and thereby to promote additional investigation; in this self-administered questionnaire, the patient reports the presence or absence of common nonmotor symptoms represented by 10 domains (i.e., gastrointestinal, urinary tract, sexual function...sleep or fatigue, pain, miscellaneous). The NMSS was developed to quantify nonmotor symptoms by severity and frequency; this scale contains 30 items grouped in nine dimensions (i.e., cardiovascular, sleep or fatigue, mood or cognition, perceptual problems...sexual function, miscellany) and is scored by the rater. Nonmotor symptoms are captured in Part I of the Movement Disorder Society-revised Unified Parkinson's Disease Rating Scale as they pertain to their impact on experiences of daily living, with six items administered by the rater and seven items answered by the patient and/or caregiver in a self-administered questionnaire. Other studies of early Parkinson's disease have utilized individual rating scales for specific nonmotor symptoms [e.g., Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Montreal Cognitive Assessment, fatigue severity scale, or Scales for Outcomes in Parkinson's disease-autonomic, to name a few] in their reports on these nonmotor symptoms.

The frequency and spectrum of nonmotor features

Nonmotor symptoms are more common in Parkinson's disease patients compared with healthy controls of similar demographics. Using global nonmotor symptoms questionnaires (e.g., NMSQuest, NMSS), multiple independent studies in incident and prevalent Parkinson's disease cohorts consistently demonstrate a high frequency of nonmotor symptoms, with number of nonmotor symptoms per individual patient ranging between 8 and 12 [36▪,37–41]. Increased drooling, urinary urgency, constipation, anxiety, forgetfulness or attentional problems, and decreased smell are among those reported across early Parkinson's disease studies. In some studies, bladder and cognitive symptoms were also common in healthy controls [36▪,40]. Frequency estimates of individual nonmotor symptoms in Parkinson's disease vary from less than 10% to over 50%. These estimates are consistent with the Parkinson and nonmotor symptoms (PRIAMO) study, a large cohort of 1072 Parkinson's disease patients spanning a broad range of disease durations and including about 10% drug-naïve [38]. In this study, 98.6% of Parkinson's disease patients reported nonmotor symptoms, with the mean number of nonmotor symptoms reported 7.8 (range 0–32).

Most commonly reported symptoms included fatigue (58%), anxiety (56%), leg pain (38%), insomnia (37%), urinary urgency and nocturia (35%), drooling (31%), and difficulty in concentrating (31%).

Increased frequency of nonmotor symptoms has been associated with the postural instability and gait disorder (PIGD) subtype of Parkinson's disease [36▪,37,40]. This suggests a common link between nondopaminergic substrates, particularly the cholinergic system, involved in motor gait disturbances and in nonmotor cognitive, affective, and autonomic issues. The total number of nonmotor symptoms significantly correlated with health-related quality of life in newly diagnosed Parkinson's disease patients in the ICICLE-PD cohort [36▪]. Here, depression, anxiety, impaired concentration, memory complaints, and sleep disturbance were specifically associated with reduced quality of life. Similarly, in the Parkinson and nonmotor symptoms study, increased cognitive, affective, and psychiatric symptoms were associated with worse quality of life [38].

Cognitive impairment

Cognitive impairment is frequent in Parkinson's disease, and studies of incident Parkinson's disease cohorts affirm that cognitive dysfunction is no longer solely a complication of advanced disease. Characteristics of the cognitive phenotype in early Parkinson's disease are mild deficits in attention, executive function, verbal fluency, and visuospatial domains, which thereby invoke dopaminergic fronto-striatal as well as nondopaminergic posterior cortically based regions (e.g., temporal, parietal). The prevalence of cognitive deficits or MCI in Parkinson's disease ranges from 19 to 36% [42–45]. In the ParkWest study in Norway, the 196 de-novo, untreated Parkinson's disease patients were more impaired across all neuropsychological tests compared with controls; the largest effect size was seen for verbal memory and one third of Parkinson's disease patients had an amnestic subtype [42]. In the CamPaiGN study of incident Parkinson's disease cases in the United Kingdom, a pattern of cognitive deficits was identified in the cases as demonstrated by impaired performance on the Mini-mental State Examination, a pattern recognition task, and the Tower of London task [44]. Using recently proposed diagnostic criteria [46], a frequency of MCI in Parkinson's disease emerged in 42.5% of the newly diagnosed, incident cases in the ICICLE-PD study; in this study, memory impairment was most commonly affected, and depression scores were higher in the cognitively impaired group [47].

Longitudinal data are now available for several of these incident Parkinson's disease cohorts with follow-up visits ranging from 3 to 10 years. From these studies, several clinical predictors of cognitive decline have been identified; in the CamPaiGN study, which has 10-year follow-up data, the most significant baseline predictors of later dementia, in addition to older age, included impaired semantic fluency and pentagon copying (hazard ratios of 3.1 and 2.6, respectively) [48,49▪▪]. Follow-up of the ParkWest cohort at 1 and 3 years revealed that patients with MCI at baseline were more likely to develop dementia than those without MCI (27% vs. 0.7%; relative risk, 39.2; 95% confidence interval, 5.2–296.5) [50]. However, at 1 year, 19% of Parkinson's disease MCI patients reverted to normal cognition, thereby suggesting that further study of the stability and progression of this cognitive state is necessary. Similarly, Broeders *et al.* [51] examined 123 Parkinson's disease patients who were newly diagnosed at baseline and then again at 3-year and 5-year follow-up. At baseline, 35% had MCI, but this rose to 53% and 50% at 3-year and 5-year follow-up, respectively. Cognitively impaired patients also had greater motor and mood symptoms.

Imaging, biological, and genetic markers provide insights regarding the etiopathogenesis of cognitive impairment in Parkinson's disease. Structural magnetic resonance studies examining gray matter volume differences between Parkinson's disease MCI patients and controls demonstrate greater atrophy in temporal (e.g., hippocampal), parietal, and frontal (e.g., prefrontal and orbitofrontal) lobe regions in patients with impaired verbal memory, decision-making, and reaction time tests [52–56], although other studies did not find gray matter differences between early Parkinson's disease patients and controls [47,52,54]. Cerebrospinal fluid measures of beta-amyloid 1–42 and 1–40 levels were reduced in de-novo Parkinson's disease patients compared with healthy controls. In the ICICLE-PD cohort, lower cerebrospinal fluid beta-amyloid 1–42 levels significantly correlated with performance on a visual pattern recognition memory task [47]. Parkinson's disease patients with the PIGD phenotype demonstrated significantly reduced cerebrospinal fluid beta-amyloid 1–42 and 1–40 levels, compared with tremor-dominant Parkinson's disease and controls in the ParkWest cohort [57]. Genetic polymorphisms may distinguish the cognitive phenotypes in early Parkinson's disease and subsequent risk for progression to dementia. Genetic analyses and longitudinal follow-up of the CamPaiGN cohort detected a variant in the microtubule-associated protein tau region that was strongly associated with earlier dementia, but the presence of a functional polymorphism in the dopamine-regulating enzyme catechol-O-methyltransferase was associated with executive dysfunction but not with dementia [48]. These biomarker studies raise questions regarding the role of amyloid and tau in cognitive impairment in Parkinson's disease, even at early stages, and risk for dementia.

Daytime sleepiness

Sleep disturbances and excessive daytime sleepiness are common problems in Parkinson's disease with multifactorial etiologies, including the disease itself, sleep-wake disruptions, and dopaminergic medications, among others. Because sedation and drowsiness are frequent side-effects of dopaminergic therapies for Parkinson's disease, Fabbrini *et al.* [58] performed a case-control study comparing the ESS and PSQI scales in de-novo, untreated Parkinson's disease to Parkinson's disease patients treated with dopaminergic medications and healthy controls. Although a small sample, the de-novo, untreated Parkinson's disease patients did not significantly differ from controls in their ESS and PSQI scores, but were significantly different from the treated Parkinson's disease patients who had the worst scores. Although excessive daytime sleepiness may result from advancing Parkinson's disease and/or side-effects of dopaminergic medications, 40 out of 158 (25%) of the de-novo Parkinson's disease patients in the ICICLE-PD study had excessive daytime sleepiness (ESS >10) [36▪]. One study using actigraphy in 18 de-novo, untreated Parkinson's disease patients reported a higher degree of sleepiness in Parkinson's disease patients compared with controls but also particularly in the hours following awakening and early afternoon [59]. Thus, sleepiness may be intrinsic to the disease even at early and unmedicated stages and relate to neurodegeneration of brainstem structures mediating sleep-wakefulness. As described in previous sections, RBD has been associated with the development of cognitive dysfunction, alone or in the context of synucleinopathies or parkinsonian disorders. Indeed, early Parkinson's disease patients with RBD and insomnia had poorer performance on cognitive test performance, even prior to initiating dopaminergic therapy [60].

Impulse control disorders

Impulse control disorders (e.g., compulsive gambling, shopping, sexual behavior, eating) are known to occur in about 14% of treated Parkinson's disease patients and strongly in association with dopaminergic therapy [61]. However, other factors may contribute to the development of impulse control disorders in Parkinson's disease, including younger age, family history of similar behaviors, and cognitive abilities. In a study evaluating 103 newly diagnosed and untreated Parkinson's disease patients, 18% were positive on screening for impulse control symptoms, as were healthy controls [62]. In this study, impulsive behaviors positively correlated with depression. Using a Parkinson's disease-specific scale for impulse control disorders, the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Short Form, Weintraub *et al.* [63] studied 168 de-novo, untreated Parkinson's disease patients and 143 healthy controls who were participants in the Parkinson's Progression Markers Initiative study. Similarly, any impulse control or related behavior was reported in 18.5% of the Parkinson's disease patients, compared with 20.3% of the controls. In multivariate analyses, increasing severity of depressive symptoms correlated with presence of impulse control or related behavior, for Parkinson's disease patients and controls, independently, although Montreal Cognitive Assessment scores did not. Findings from these two studies suggest that Parkinson's disease alone does not necessarily confer an increased risk of impulse control disorders; however, longitudinal studies are needed to determine how dopaminergic treatment will affect behaviors of those untreated patients endorsed impulse control behaviors at baseline.

Autonomic and sensory symptoms

Autonomic features frequently accompany early and untreated Parkinson's disease. In several studies utilizing comprehensive nonmotor scales, drooling [36▪,37,40], urinary urgency [36▪,37,40], or nocturia [41], and constipation [36▪,37,40] were frequent, occurring in about 40–60% of patients. In 275 newly diagnosed, untreated Parkinson's disease patients from the ParkWest cohort, drooling was the most common nonmotor symptom (42%) and sensory complaints occurred in 34% [37]. Increased heart rates have been found on routine electrocardiograms in de-novo Parkinson's disease patients, compared with healthy controls, in the De Novo Parkinson study [64]. In most of these studies, the autonomic symptoms were significantly more common in Parkinson's disease patients compared with controls. However, Kim *et al.* [41] found that nocturia was also common in their control group (47.8% in controls vs. 65.2% in Parkinson's disease), although the sample size was small, and Muller *et al.* [37] did not find any difference in increased sweating between Parkinson's disease patients and controls. Despite the high prevalence of the autonomic and sensory symptoms, Muller *et al.* [37] found that daily activities were not affected by these symptoms in 58% of patients and they were rated as 'mild' in the majority. In two large studies of incident, untreated Parkinson's disease patients (i.e., ParkWest and ICICLE-PD cohorts), autonomic symptoms were greater in those Parkinson's disease patients with the PIGD phenotype, compared with tremor-dominant patients [37,40]. After correction for multiple comparisons, drooling and dribbling were significantly more common in PIGD patients (67%), compared with tremor-dominant patients (33%) [36■].

Presence of autonomic and sensory symptoms in early and de-novo Parkinson's disease invokes involvement of the peripheral and central nervous system consistent with the proposed progressive neurodegenerative changes by Braak *et al.* [65]. Although there are many explanations for increased drooling in Parkinson's disease, it is interesting to note the detection of Lewy bodies within the submandibular salivary gland [66]. In addition, impaired heart rate variability may reflect autonomic dysregulation because of Lewy bodies within cardiac neurons [67■■].

CONCLUSION

Nonmotor features of Parkinson's disease are common, associated with poor outcomes, implicate several nondopaminergic systems, and await improved therapeutics. Large observational studies with longitudinal follow-up of incident Parkinson's disease patients provide the basis for advancing our understanding of the progression of nonmotor symptoms, their impact on patients, underlying neurobiological mechanisms, and the role of biomarkers. Nonmotor symptoms that occur in the prodromal phase of Parkinson's disease are now being studied in specific premotor cohorts. Incorporating clinical and biomarker risk factors in these Parkinson's disease contexts may lead to earlier identification of patients at risk for developing Parkinson's disease or its complications and ultimately, neuroprotective and disease-modifying therapies.

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Conflicts of interest

There are no conflicts of interest.

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This article reviews the neuropathology and anatomy of Lewy pathology-related neurodegeneration in the context of nonmotor features of Parkinson's disease and prodromal phases.