Published in final edited form as:
Curr Opin Neurol. 2014 August ; 27(4): 434–441. doi:10.1097/WCO.0000000000000112.

Premotor and non-motor features of Parkinson's disease

Jennifer G. Goldman, MD, MS[1] and **Ron Postuma, MD, MSc**[2]

[1]Rush University Medical Center, Department of Neurological Sciences, Section of Parkinson Disease and Movement Disorders, Chicago IL, USA

[2]McGill University, Montreal General Hospital, Department of Neurology, Montreal, Canada

Abstract

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

Recent findings—While Parkinson's disease patients experience a wide range of non-motor symptoms throughout the disease course, studies demonstrate that non-motor 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 non-motor symptoms such as cognitive impairment are now recognized in incident or de novo Parkinson's disease cohorts. Many of these non-motor features reflect disturbances in non-dopaminergic 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 on the frequency, pathophysiology, and importance of non-motor features in Parkinson's disease as well as the recognition that these non-motor 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 multi-system disorder with motor and non-motor 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

Corresponding author: Contact details: Jennifer G. Goldman, MD, MS, Rush University Medical Center, Department of Neurological Sciences, Section of Parkinson Disease and Movement Disorders, 1725 W. Harrison Street, Suite 755, Chicago, IL 60612, Telephone: 312-563-2900, Fax: 312-563-2024, Jennifer_G_Goldman@rush.edu.

Conflicts of interest
There are no conflicts of interest

also serotonergic and noradrenergic brainstem areas, cholinergic frontal and brainstem regions, among others. From observational and longitudinal studies, several non-motor 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 non-motor 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 non-motor 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/when we might be able to intervene with neuroprotective or disease-modifying therapies.[1, 2] This review will discuss recent advances in premotor and non-motor features in Parkinson's disease, focusing on these issues in the context of prodromal and early stage Parkinson's disease.

PREMOTOR SYMPTOMS AS A PRODROME TO PARKINSON'S DISEASE

REM Sleep Behavior Disorder

Of all clinical markers, REM sleep behavior disorder (RBD) is, by far, associated with the highest PD risk. The original description of RBD as a prodromal marker reported that 38% developed PD 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 follow-up (a rate that also includes 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 PD.[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 PD 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 PD 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 SPECT,[10] olfaction,[11] decreased color vision,[11] and subtle motor dysfunction[12] can serve as prodromal markers of PD/DLB.

Olfaction

Up to 85% of patients with PD 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 PD. Moreover, those in the lowest tertile of olfaction function had an 11-fold odds of having incidental Lewy bodies on autopsy, even without established PD.[14] A Dutch study examined family members of PD patients and found that those with hyposmia had greater dopaminergic denervation on functional neuroimaging. Moreover, 4/40 patients with in the lowest decile of olfactory function developed PD over the next two years, compared to 0/360 with preserved olfaction.[15] In the Prospective Validation of Risk factors for the development of Parkinson Syndromes (PRIPS) study, a prospective population-based follow-up of 1850 subjects, impaired olfaction was associated with a 3.94 odds ratio of developing PD.[16] In the Parkinson Associated Risk Study (PARS) study, olfactory loss has been associated with other potential markers of prodromal PD, including constipation, anxiety, depression and dream-enactment behavior (i.e probable REM sleep behavior disorder) 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 3-fold increased risk of developing PD/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 four years of follow-up. Similarly, the Dutch cohort found that only one additional patient with hyposmia developed PD in the second 3-year follow-up.[18] This may suggest that olfactory loss becomes apparent only 2–5 years before motor PD. 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 PD is low. To illustrate, all of the patients in the lowest olfactory quartile of the Honoulu Asia Aging study had anosmia, but only 10/549 developed disease.[13]

Constipation

There is increasing evidence that constipation can identify prodromal PD. In manifest PD, 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/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 to an iLBD prevalence of 12% in the study population.[21] A recent study described deposition of colonic synuclein in 3 PD patients from colonoscopy samples taken 2–5 years before diagnosis of clinical PD.[22] However, sensitivity and specificity remain unclear; in an autopsy study, Beach *et al* described gastrointestinal synuclein deposition in only 20% of patients with iLBD,[20] suggesting that sensitivity may be low.

Clinically, there is also prospective evidence that constipation can precede PD. Consistent with their findings in iLBD, the Honolulu Asia Aging study found that men with bowel movement frequencies <1 per day were at 2–5-fold increased risk of developing PD in the future. Savica *et al* found that constipation as documented in medical records was associated with a 2.5-fold increased odds of PD.[23] Finally, Gao *et al* found that bowel movement frequency <3 per week was associated with a 5-fold increased risk of PD in men, and a 2.2-fold increase in women[24]. Of interest, both the Honolulu and Savica studies found constipation >15 years before PD 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 PD, 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 PD diagnosis had an 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 PD; however, this relationship was strongest for the first two years, suggesting a relatively short prodromal interval.[26] Fang *et al*, analyzing data from the National Institute of Healthy-American Association of Retired Persons (NIH-AARP) Diet and Health Study follow-up survey found that patients diagnosed with PD had a 2.7-fold odds ratio of depression in the 1–5 years preceding diagnosis.[27] This relationship was also present even at intervals of greater than 15 years before PD diagnosis (OR=1.8). Anxiety and depression are closely linked in PD, suggesting 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 PD, 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 a OR of 1.6 for development of PD, a relationship that was present for very long prodromal intervals.[29] Related to anxiety, there is some evidence of a PD 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, since studies have described differences even in young adulthood.

NON-MOTOR FEATURES IN EARLY PARKINSON'S DISEASE

Although the number and severity of non-motor symptoms increases 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. Non-motor 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 non-

motor 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, ICICLE in the United Kingdom, CamPaiGN in United Kingdom, and DeNoPa in Germany, among others) and several of these studies are discussed in this review. In a large retrospective review of pathologically confirmed cases, non-motor 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 non-motor 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 non-motor symptoms. These include the Nonmotor Symptom Questionnaire (NMSQuest),[33] Nonmotor Symptoms Scale (NMSS),[34] Movement Disorder Society-revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[35] as well as individual rating scales for specific non-motor 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 non-motor symptoms over the past month and thereby promote additional investigation; in this self-administered questionnaire, the patient reports the presence/absence of common non-motor symptoms represented by 10 domains (i.e., gastrointestinal, urinary tract, sexual function…sleep/fatigue, pain, miscellaneous). The NMSS was developed to quantify non-motor symptoms by severity and frequency; this scale contains 30 items grouped in 9 dimensions (i.e., cardiovascular, sleep/fatigue, mood/cognition, perceptual problems…sexual function, miscellany) and is scored by the rater. Non-motor symptoms are captured in Part I of the MDS-UPDRS as they pertain to their impact on experiences of daily living, with 6 items administered by the rater and 7 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 non-motor symptoms (e.g., Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Montreal Cognitive Assessment (MoCA), Fatigue Severity Scale, or SCOPA-autonomic scale, to name a few) in their reports on these non-motor symptoms.

The frequency and spectrum of non-motor features

Non-motor symptoms are more common in Parkinson's disease patients compared to healthy controls of similar demographics. Using global non-motor symptoms questionnaires (e.g., NMSQuest, NMSS), multiple independent studies in incident and prevalent Parkinson's disease cohorts consistently demonstrate a high frequency of non-motor symptoms, with number of non-motor symptoms per individual patient ranging between 8–12.[36–41] 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 non-motor symptoms in Parkinson's disease vary from < 10% to over 50%. These estimates are consistent with the

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 non-motor symptoms, with the mean number of non-motor 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 concentrating (31%).

Increased frequency of non-motor symptoms has been associated with the postural instability and gait difficulty (PIGD) subtype of Parkinson's disease. [36, 37, 40] This suggests a common link between non-dopaminergic substrates, particularly the cholinergic system, involved in motor gait disturbances and in non-motor cognitive, affective, and autonomic issues. The total number of non-motor symptoms significantly correlated with health-related quality of life in newly diagnosed Parkinson's disease patients in the ICICLE cohort.[36] Here, depression, anxiety, impaired concentration, memory complaints and sleep disturbance were specifically associated with reduced quality of life. Similarly, in the PRIAMO 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. Characteristic 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 non-dopaminergic posterior cortically-based regions (temporal, parietal). The prevalence of cognitive deficits or mild cognitive impairment in Parkinson's disease ranges from 19–36%.[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 to controls; the largest effect size was seen for verbal memory and 1/3rd 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 with 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 mild cognitive impairment in Parkinson's disease emerged in 42.5% of the newly diagnosed, incident cases in the ICICLE study; in this study memory impairment was most commonly affected, and depression scores were higher in the cognitively impaired group.[47]

Longitudinal data is 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 mild cognitive impairment at baseline were more likely to develop dementia than those without mild cognitive impairment (27% vs. 0.7%, relative risk 39.2, 95% CI,

5.2–296.5).[50] However, at one year, 19% of Parkinson's disease mild cognitive impairment 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* examined 123 Parkinson's disease patients who were newly diagnosed at baseline and then again at 3 and 5 year follow-up.[51] At baseline, 35% had mild cognitive impairment, but this rose to 53% and 50% at 3 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 mild cognitive impairment 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] though 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 to healthy controls. In the ICICLE 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 to 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 (MAPT) tau region that was strongly associated with earlier dementia, but the presence of a functional polymorphism in the dopamine regulating enzyme catechol-O-methyltransferase (COMT) 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 multi-factorial etiologies, including the disease itself, sleep-wake disruptions, and dopaminergic medications, among others. Since sedation and drowsiness are frequent side effects of dopaminergic therapies for Parkinson's disease, Fabbrini *et al* 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.[58] Although a small sample, 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. While excessive daytime sleepiness may result from advancing Parkinson's disease and/or side effects of dopaminergic medications, 40/158 (25%) of the de novo Parkinson's disease patients in the ICICLE 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 to 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/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 (QUIP)-Short Form, Weintraub *et al* studied 168 de novo, untreated Parkinson's disease patients and 143 healthy controls who were participants in the Parkinson's Progression Markers Initiative study.[63] Similarly, any impulse control or related behavior was reported in 18.5% of the Parkinson's disease patients, compared to 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, though MoCA 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 non-motor 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 non-motor 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 to healthy controls, in the DeNoPa study.[64] In most of these studies, the autonomic symptoms were significantly more common in Parkinson's disease patients compared to controls. However, Kim *et al* found that nocturia was also common in their control group (47.8% in controls vs. 65.2% in Parkinson's disease), though the sample size was small,[41] and Muller *et al* did not find a difference in increased sweating between Parkinson's disease patients and controls.[37] Despite the high prevalence of the autonomic and sensory symptoms, Muller *et al* found that

daily activities were not affected by these symptoms in 58% of patients and they were rated as “mild” in the majority. [37] In two large studies of incident, untreated Parkinson’s disease patients (i.e., ParkWest and ICICLE cohorts), autonomic symptoms were greater in those Parkinson’s disease patients with the postural instability gait disorder (PIGD) phenotype, compared to tremor-dominant patients.[37, 40] After correction for multiple comparisons, drooling and dribbling were significantly more common in PIGD patients (67%), compared to 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 due to Lewy body pathology within cardiac neurons.[67]

CONCLUSIONS

Non-motor features of Parkinson’s disease are common, associated with poor outcomes, implicate several non-dopaminergic 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 non-motor symptoms, their impact on patients, underlying neurobiological mechanisms, and the role of biomarkers. Non-motor symptoms that occur in the prodromal phase of Parkinson’s disease are now being studied in prodromal 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.

REFERENCES AND RECOMMENDED READING

• of special interest

•• of outstanding interest

1•. Berg D, Postuma RB, Bloem B, Chan P, Dubois B, Gasser T, et al. Time to redefine PD? Introductory statement of the MDS Task Force on the definition of Parkinson’s disease. Mov Disord. 2014; 29(4):454–62. This article provides a thought-provoking discussion on redefining Parkinson’s disease. [PubMed: 24619848]

2••. Siderowf A, Lang AE. Premotor Parkinson’s disease: concepts and definitions. Mov Disord. 2012; 27(5):608–16. This review describes different phases of classifying premotor Parkinson’s disease and potential diagnostic issues. [PubMed: 22508279]

3. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older males initially diagnosed with idiopathic REM sleep behavior disorder (RBD): 16year update on a previously reported series. Sleep Med. 2013

4•. Iranzo A, Tolosa E, Gelpi E, Molinuevo JL, Valldeoriola F, Serradell M, et al. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. Lancet Neurol. 2013; 12(5):443–53. This study demonstrates that most idiopathic RBD patients develop a Lewy body disorder and that this sleep

disturbance is a candidate for studying prodromal Parkinson's disease with accompanying imaging biomarkers and pathological studies. [PubMed: 23562390]

5. Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, Montplaisir J. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. Neurology. 2009; 72(15):1296–300. [PubMed: 19109537]
6. Wing YK, Li SX, Mok V, Lam SP, Tsoh J, Chan A, et al. Prospective outcome of rapid eye movement sleep behaviour disorder: psychiatric disorders as a potential early marker of Parkinson's disease. J Neurol Neurosurg Psychiatry. 2012; 83(4):470–2. [PubMed: 22250185]
7. Postuma RB, Gagnon JF, Tuineaig M, Bertrand JA, Latreille V, Desjardins C, et al. Antidepressants and REM Sleep Behavior Disorder: Isolated Side Effect or Neurodegenerative Signal? Sleep. 2013; 36(11):1579–85. [PubMed: 24179289]
8. Boot BP, Boeve BF, Roberts RO, Ferman TJ, Geda YE, Pankratz VS, et al. Probable rapid eye movement sleep behavior disorder increases risk for mild cognitive impairment and Parkinson disease: a population-based study. Ann Neurol. 2012; 71(1):49–56. [PubMed: 22275251]
9. Iranzo A, Lomena F, Stockner H, Valldeoriola F, Vilaseca I, Salamero M, et al. Decreased striatal dopamine transporters uptake and substantia nigra hyperechogenicity as risk markers of synucleinopathy in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study. Lancet Neurol. 2010; 9(11):1070–7. [PubMed: 20846908]
10. Dang-Vu TT, Gagnon JF, Vendette M, Soucy JP, Postuma RB, Montplaisir J. Hippocampal perfusion predicts impending neurodegeneration in REM sleep behavior disorder. Neurology. 2012; 79(24):2302–6. [PubMed: 23115214]
11. Postuma RB, Gagnon JF, Vendette M, Desjardins C, Montplaisir J. Olfaction and Color Vision Identify Impending Neurodegeneration in REM behavior disorder. AnnNeurol. 2011; 69(5):811–8.
12. Postuma RB, Lang AE, Gagnon JF, Pelletier A, Montplaisir JY. How does parkinsonism start? Prodromal parkinsonism motor changes in idiopathic REM sleep behaviour disorder. Brain. 2012; 135(Pt 6):1860–70. [PubMed: 22561644]
13. Ross W, Petrovitch H, abbott RD, Tanner C, Popper J, Masaki K, et al. Association of olfactory dysfunction with risk of future Parkinson's disease. Movement Disorders. 2005; 20(Supplement 10):S129–S30.
14. Ross GW, Abbott RD, Petrovitch H, Tanner CM, Davis DG, Nelson J, et al. Association of olfactory dysfunction with incidental Lewy bodies. Mov Disord. 2006; 21(12):2062–7. [PubMed: 16991138]
15. Ponsen MM, Stoffers D, Booij J, van Eck-Smit BL, Wolters EC, Berendse HW. Idiopathic hyposmia as a preclinical sign of Parkinson's disease. AnnNeurol. 2004; 56(2):173–81.
16. Berg D, Marek K, Ross GW, Poewe W. Defining at-risk populations for Parkinson's disease: lessons from ongoing studies. Mov Disord. 2012; 27(5):656–65. [PubMed: 22508284]
17•. Siderowf A, Jennings D, Eberly S, Oakes D, Hawkins KA, Ascherio A, et al. Impaired olfaction and other prodromal features in the Parkinson At-Risk Syndrome Study. Mov Disord. 2012; 27(3):406–12. This large study of 4999 subjects examines the association between impaired olfaction and other prodromal features of Parkinson's disease, highlighting the role of hyposmia as a marker of future neurodegeneration. [PubMed: 22237833]
18. Ponsen MM, Stoffers D, Twisk JW, Wolters EC, Berendse HW. Hyposmia and executive dysfunction as predictors of future Parkinson's disease: a prospective study. Mov Disord. 2009; 24(7):1060–5. [PubMed: 19353591]
19. Pouclet H, Lebouvier T, Coron E, des Varannes SB, Rouaud T, Roy M, et al. A comparison between rectal and colonic biopsies to detect Lewy pathology in Parkinson's disease. Neurobiol Dis. 2012; 45(1):305–9. [PubMed: 21878391]
20. Beach TG, Adler CH, Sue LI, Vedders L, Lue L, White CL III, et al. Multi-organ distribution of phosphorylated alpha-synuclein histopathology in subjects with Lewy body disorders. Acta Neuropathol. 2010; 119(6):689–702. [PubMed: 20306269]
21. Abbott RD, Ross GW, Petrovitch H, Tanner CM, Davis DG, Masaki KH, et al. Bowel movement frequency in late-life and incidental Lewy bodies. Mov Disord. 2007; 22(11):1581–6. [PubMed: 17523195]

22•. Shannon KM, Keshavarzian A, Dodiya HB, Jakate S, Kordower JH. Is alpha-synuclein in the colon a biomarker for premotor Parkinson's disease? Evidence from 3 cases. Mov Disord. 2012; 27(6):716–9. This study reports alpha-synuclein deposition in colonic biopsies as a possible biomarker for Parkinson's disease. [PubMed: 22550057]

23. Savica R, Carlin JM, Grossardt BR, Bower JH, Ahlskog JE, Maraganore DM, et al. Medical records documentation of constipation preceding Parkinson disease: A case-control study. Neurology. 2009; 73(21):1752–8. [PubMed: 19933976]

24. Gao X, Chen H, Schwarzschild MA, Ascherio A. A prospective study of bowel movement frequency and risk of Parkinson's disease. Am J Epidemiol. 2011; 174(5):546–51. [PubMed: 21719744]

25. Leentjens AF, Van den AM, Metsemakers JF, Lousberg R, Verhey FR. Higher incidence of depression preceding the onset of Parkinson's disease: a register study. Mov Disord. 2003; 18(4): 414–8. [PubMed: 12671948]

26. Alonso A, Rodriguez LA, Logroscino G, Hernan MA. Use of antidepressants and the risk of Parkinson's disease: a prospective study. J Neurol Neurosurg Psychiatry. 2009; 80(6):671–4. [PubMed: 19448091]

27. Fang F, Xu Q, Park Y, Huang X, Hollenbeck A, Blair A, et al. Depression and the subsequent risk of Parkinson's disease in the NIH-AARP Diet and Health Study. Mov Disord. 2010; 25(9):1157–62. [PubMed: 20310050]

28. Weisskopf MG, Chen H, Schwarzschild MA, Kawachi I, Ascherio A. Prospective study of phobic anxiety and risk of Parkinson's disease. Mov Disord. 2003; 18(6):646–51. [PubMed: 12784267]

29. Bower JH, Grossardt BR, Maraganore DM, Ahlskog JE, Colligan RC, Geda YE, et al. Anxious personality predicts an increased risk of Parkinson's disease. Mov Disord. 2010; 25(13):2105–13. [PubMed: 20669309]

30. Ishihara L, Brayne C. What is the evidence for a premorbid parkinsonian personality: a systematic review. Mov Disord. 2006; 21(8):1066–72. [PubMed: 16755553]

31. Menza MA, Golbe LI, Cody RA, Forman NE. Dopamine-related personality traits in Parkinson's disease. Neurology. 1993; 43(3 Pt 1):505–8. [PubMed: 8450991]

32. O'Sullivan SS, Williams DR, Gallagher DA, Massey LA, Silveira-Moriyama L, Lees AJ. Nonmotor symptoms as presenting complaints in Parkinson's disease: a clinicopathological study. Mov Disord. 2008; 23(1):101–6. [PubMed: 17994582]

33. Chaudhuri KR, Martinez-Martin P, Schapira AH, Stocchi F, Sethi K, Odin P, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. Mov Disord. 2006; 21(7):916–23. [PubMed: 16547944]

34. Chaudhuri KR, Martinez-Martin P, Brown RG, Sethi K, Stocchi F, Odin P, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: Results from an international pilot study. Mov Disord. 2007; 22(13):1901–11. [PubMed: 17674410]

35. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008; 23(15):2129–70. [PubMed: 19025984]

36•. Duncan GW, Khoo TK, Yarnall AJ, O'Brien JT, Coleman SY, Brooks DJ, et al. Health-related quality of life in early Parkinson's disease: the impact of nonmotor symptoms. Mov Disord. 2014; 29(2):195–202. In this study of newly diagnosed Parkinson's disease patients compared to healthy controls, non-motor symptoms significantly reduced healthy-related quality of life in Parkinson's disease. [PubMed: 24123307]

37. Muller B, Larsen JP, Wentzel-Larsen T, Skeie GO, Tysnes OB. Autonomic and sensory symptoms and signs in incident, untreated Parkinson's disease: frequent but mild. Mov Disord. 2011; 26(1): 65–72. [PubMed: 20925070]

38. Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, et al. The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord. 2009; 24(11):1641–9. [PubMed: 19514014]

39. Erro R, Picillo M, Vitale C, Amboni M, Moccia M, Longo K, et al. Non-motor symptoms in early Parkinson's disease: a 2-year follow-up study on previously untreated patients. J Neurol Neurosurg Psychiatry. 2013; 84(1):14–7. [PubMed: 22993448]
40. Khoo TK, Yarnall AJ, Duncan GW, Coleman S, O'Brien JT, Brooks DJ, et al. The spectrum of nonmotor symptoms in early Parkinson disease. Neurology. 2013; 80(3):276–81. [PubMed: 23319473]
41. Kim HJ, Park SY, Cho YJ, Hong KS, Cho JY, Seo SY, et al. Nonmotor symptoms in de novo Parkinson disease before and after dopaminergic treatment. J Neurol Sci. 2009; 287(1–2):200–4. [PubMed: 19700173]
42. Aarsland D, Bronnick K, Larsen JP, Tysnes OB, Alves G. Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. Neurology. 2009; 72(13):1121–6. [PubMed: 19020293]
43. Elgh E, Domellof M, Linder J, Edstrom M, Stenlund H, Forsgren L. Cognitive function in early Parkinson's disease: a population-based study. Eur J Neurol. 2009; 16(12):1278–84. [PubMed: 19538208]
44. Foltynie T, Brayne CE, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain. 2004; 127(Pt 3):550–60. [PubMed: 14691062]
45. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology. 2005; 65(8):1239–45. [PubMed: 16247051]
46. Litvan I, Goldman JG, Troster AI, Schmand BA, Weintraub D, Petersen RC, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord. 2012; 27(3):349–56. [PubMed: 22275317]
47. Yarnall AJ, Breen DP, Duncan GW, Khoo TK, Coleman SY, Firbank MJ, et al. Characterizing mild cognitive impairment in incident Parkinson disease: the ICICLE-PD study. Neurology. 2014; 82(4):308–16. [PubMed: 24363137]
48. Williams-Gray CH, Evans JR, Goris A, Foltynie T, Ban M, Robbins TW, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. Brain. 2009; 132(Pt 11):2958–69. [PubMed: 19812213]
49••. Williams-Gray CH, Mason SL, Evans JR, Foltynie T, Brayne C, Robbins TW, et al. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. J Neurol Neurosurg Psychiatry. 2013; 84(11):1258–64. This study provides 10-year follow up data on the CamPaIGN incident cohort of Parkinson's disease patients, reporting a heterogenous evolution of Parkinson's disease, reasons for death, and clinical and genetic predictors of dementia. [PubMed: 23781007]
50. Pedersen KF, Larsen JP, Tysnes OB, Alves G. Prognosis of Mild Cognitive Impairment in Early Parkinson Disease: The Norwegian ParkWest Study. JAMA Neurol. 2013:1–7.
51. Broeders M, de Bie RM, Velseboer DC, Speelman JD, Muslimovic D, Schmand B. Evolution of mild cognitive impairment in Parkinson disease. Neurology. 2013; 81(4):346–52. [PubMed: 23794682]
52. Apostolova LG, Beyer M, Green AE, Hwang KS, Morra JH, Chou YY, et al. Hippocampal, caudate, and ventricular changes in Parkinson's disease with and without dementia. Mov Disord. 2010; 25(6):687–8. [PubMed: 20437538]
53. Bruck A, Kurki T, Kaasinen V, Vahlberg T, Rinne JO. Hippocampal and prefrontal atrophy in patients with early non-demented Parkinson's disease is related to cognitive impairment. J Neurol Neurosurg Psychiatry. 2004; 75(10):1467–9. [PubMed: 15377698]
54. Dalaker TO, Zivadinov R, Larsen JP, Beyer MK, Cox JL, Alves G, et al. Gray matter correlations of cognition in incident Parkinson's disease. Mov Disord. 2010; 25(5):629–33. [PubMed: 20213820]
55. Hattori T, Orimo S, Aoki S, Ito K, Abe O, Amano A, et al. Cognitive status correlates with white matter alteration in Parkinson's disease. Hum Brain Mapp. 2012; 33(3):727–39. [PubMed: 21495116]

56. Song SK, Lee JE, Park HJ, Sohn YH, Lee JD, Lee PH. The pattern of cortical atrophy in patients with Parkinson's disease according to cognitive status. Mov Disord. 2011; 26(2):289–96. [PubMed: 21370255]
57. Alves G, Pedersen KF, Bloem BR, Blennow K, Zetterberg H, Borm GF, et al. Cerebrospinal fluid amyloid-beta and phenotypic heterogeneity in de novo Parkinson's disease. J Neurol Neurosurg Psychiatry. 2013; 84(5):537–43. [PubMed: 23117496]
58. Fabbrini G, Barbanti P, Aurilia C, Vanacore N, Pauletti C, Meco G. Excessive daytime sleepiness in de novo and treated Parkinson's disease. Mov Disord. 2002; 17(5):1026–30. [PubMed: 12360553]
59. Giganti F, Ramat S, Zilli I, Guidi S, Raglione L, Sorbi S, et al. Daytime course of sleepiness in de novo Parkinson's diseae patients. J Sleep Res. 2013; 22:197–200. [PubMed: 23137353]
60. Erro R, Santangelo G, Picillo M, Vitale C, Amboni M, Longo K, et al. Link between non-motor symptoms and cognitive dysfunctions in de novo, drug-naive PD patients. J Neurol. 2012; 259(9): 1808–13. [PubMed: 22310940]
61. Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol. 2010; 67(5): 589–95. [PubMed: 20457959]
62. Antonini A, Siri C, Santangelo G, Cilia R, Poletti M, Canesi M, et al. Impulsivity and compulsivity in drug-naive patients with Parkinson's disease. Mov Disord. 2011; 26(3):464–8. [PubMed: 21312278]
63. Weintraub D, Papay K, Siderowf A. Screening for impulse control symptoms in patients with de novo Parkinson disease: a case-control study. Neurology. 2013; 80(2):176–80. [PubMed: 23296128]
64. Mollenhauer B, Trautmann E, Sixel-Doring F, Wicke T, Ebentheuer J, Schaumburg M, et al. Nonmotor and diagnostic findings in subjects with de novo Parkinson disease of the DeNoPa cohort. Neurology. 2013; 81(14):1226–34. [PubMed: 23997153]
65. Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res. 2004; 318(1):121–34. [PubMed: 15338272]
66. Del Tredici K, Hawkes CH, Ghebremedhin E, Braak H. Lewy pathology in the submandibular gland of individuals with incidental Lewy body disease and sporadic Parkinson's disease. Acta Neuropathol. 2010; 119(6):703–13. [PubMed: 20229352]
67••. Del Tredici K, Braak H. Lewy pathology and neurodegeneration in premotor Parkinson's disease. Mov Disord. 2012; 27(5):597–607. This article reviews the neuropathology and anatomy of Lewy pathology-related neurodegeneration in the context of non-motor features of Parkinson's disease and prodromal phases. [PubMed: 22508278]

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.
- Non-motor features accompany all stages of Parkinson's disease, from prodromal to early and advanced disease, frequently reflect underlying non-dopaminergic mechanisms, and substantially impact patients' quality of life.