Movement Disorders
CLINICAL PRACTICE
REVIEW

Characterizing Premotor Parkinson's Disease: Clinical Features and Objective Markers

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Abstract: Increasingly, it has been recognized that in order to affect underlying neurodegeneration in Parkinson's disease (PD), individuals must be identified before onset of the classic motor symptoms. Thus, for research purposes, a redefinition of PD has been proposed into preclinical, premotor, and motor phases. In the preclinical phase, no clinical signs or symptoms of PD are present. In the premotor phase, nonmotor manifestations are detectable. These include olfactory, neuropsychiatric, sleep, gastrointestinal, and autonomic changes. A multi-modal approach is needed to maximize both sensitivity and specificity of any assessment of the premotor phase. To that end, several objective markers, such as dopaminergic imaging and electrophysiologic techniques, exist and are of potential utility. This review discusses the candidate nonmotor features and potential objective measures that may be used to define the premotor phase of PD.

In the nearly 200 years since Parkinson's disease (PD) was first described, extensive clinical characterization of the signs and symptoms, along with clinicopathological correlation, have allowed for the establishment of robust clinical criteria for diagnosis.[1] However, it is becoming increasingly clear, in the face of multiple failed disease-modification trials, that it is essential that we detect PD earlier, before motor manifestations are present. Thus, for research purposes, a redefinition of PD into three phases, particularly on research grounds, has been put forth.[2,3] These three phases include preclinical, premotor, and motor phases (Table 1). Whether some of the premotor manifestations result from neurodegeneration or are truly premorbid (preceding onset of neurodegeneration), is unclear, though, at least in some cases, evidence suggests the former, as detailed below. Note that the three phases do not necessarily occur in the same chronological order in individual PD patients, and not all may be present.[3] Thus, extensive characterization of each phase is essential. Exciting data have begun to emerge from the cohorts of individuals thought to be "at risk" of PD that have been assembled by us and others to achieve this goal.[4] This review will focus on the premotor phase of PD, namely, the phase of PD in which nonmotor signs and symptoms are present, and are hypothesized to result from extranigral pathology (Table 1). These include various clinical, imaging, and electrophysiological features (Table 2). We will then discuss the need for multimodal biomarkers to further characterize the premotor syndrome and discuss advances in imaging and other tools for identifying premotor PD.

Olfactory Dysfunction

Over 90% of patients with PD have olfactory dysfunction,[5] manifesting as deficits of odor identification, discrimination, and threshold.[26–28] There are extensive data to support the incorporation of olfactory loss as a feature of premotor PD. One of the most robust lines of evidence comes from the Honolulu-Asia Aging Study (HAAS).[8] In this longitudinal study of 2,267 men without PD, olfaction was assessed with the Brief Smell Identification Test.[29] A relative odds of 5.2 for the development of PD was found among those scoring in the lowest quartile of odor identification.[8]

Another approach to assessing the association between olfaction and premotor PD involves the prospective assessment of first-degree relatives of PD patients. In one such study,[6] 361 asymptomatic first-degree relatives of PD patients were screened for olfactory deficits, and 40 hyposmics and 38 normosmics were identified to undergo dopamine transporter single-photon emission computed tomography with [^{123}I]-fluoropropyl (FP)-β-CIT (DAT-SPECT). Four of the forty hyposmic relatives and none of the normosmic relatives developed PD within

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TABLE 1 Proposed redefinition of PD[2,3]

	Features	Comments
Phase 1: preclinical	No clinical signs or symptoms of PD are present.	PD-specific pathology assumed to be present; supported by genetic, molecular, or imaging biomarkers of the disease
Phase 2: premotor	A pure nonmotor phase comprising early premotor signs or symptoms	Hypothesized to correspond to Braak stages 2 (e.g., proposed to result from extranigral PD pathology)
Phase 3: motor	Classic motor manifestations of PD are present.	Hypothesized to correspond to Braak stages 3 to 6 (e.g., PD pathology involving the SN, leading to nigrostriatal dopamine deficiency sufficient to cause classic motor manifestations, followed later by additional nonmotor features because of extension of the pathology)

2 years of initial assessment; all those that developed PD also had associated reduced striatal binding ratios at baseline,[6] indicative of subclinical dopaminergic system degeneration. An abnormality of odor discrimination was the best predictor of future risk of PD.[30] The 5-year risk of developing PD among first-degree relatives of PD patients with unexplained olfactory deficits was estimated at 12.5%.[7]

Despite these data, it is important to note that olfactory loss is observed in several other neurodegenerative parkinsonian[28] and nonparkinsonian disorders, including Alzheimer's disease (AD).[31] Thus, its incorporation into premotor criteria needs to occur in conjunction with other, more specific tests, such as imaging or other biomarkers, as detailed further below.

Personality, Psychiatric, and Cognitive Manifestations

Studies have suggested that certain personality traits, psychiatric symptoms, and psychiatric disorders are part of the premotor phase of PD. It is not yet clear whether these are risk factors or risk markers for PD. A specific personality trait could lead to selection of a certain occupation or other lifestyle choices that lead to exposure to environmental factors that themselves increase risk of PD. On the other hand, these neuropsychiatric manifestations may be the earliest manifestations of the disease itself.

Premorbid Personality

Most studies have investigated premorbid personality by studying patients with motor PD. Structured interviews and validated personality inventories were used. Individuals with PD have a history of stoicism and are less likely to be novelty seeking, as compared to controls.[32–34] Other personality traits described in PD patients include conscientiousness, cautiousness, rigidity, dependence, skepticism, and subordination.[14] Of note, studies comparing PD patients to patients with other chronic neurological disorders, including essential tremor and AD, have not consistently shown differences in premorbid personality. Thus, the diagnosis of a chronic disease may introduce recall bias or other factors that confound studies of premorbid personality.[14] Before specific personality traits are incorporated into the premotor PD syndrome, the premorbid personality needs to be studied in patients without a diagnosis of PD who are followed prospectively and subsequently go on to develop PD; the preclinical and premorbid PD cohorts being followed[4] are a prime opportunity for this.

Depression and Anxiety

Several studies support inclusion of depression in the premotor PD syndrome.[35] One example is a retrospective, register-based study of 338 PD cases and 32,007 age- and gender-matched controls. It demonstrated that PD patients had 2.4 times the odds of having a history of depression, as compared to controls, with the first depressive episode preceding the diagnosis of PD by an average of 10 years.[15] Another retrospective cohort study[16] of 4,636 patients with depression and 18,544 control patients without depression found that those with depression had 3.24 times the odds of being diagnosed with PD. Importantly, similar results were found after excluding those in which depression was diagnosed within 2 and 5 years of PD, suggesting an increased long-term risk of PD in patients with depression.[16]

Data supporting inclusion of anxiety as part of the premotor PD syndrome is also available, but less robust.[35] In the Health Professionals' Follow-Up Study (HPFS),[17] 35,815 males were administered a validated self-rating inventory that assesses personality trains and symptoms of phobic anxiety. They were followed and PD cases prospectively ascertained. Over the time of the follow-up (which was until diagnosis of PD or up to 22 years), 189 PD cases were identified. There was a significant relationship between the level of phobic anxiety and risk of PD. For each unit increase in the anxiety index score, the relative risk of PD was 1.1. In order to assess whether the anxiety was a manifestation of undiagnosed PD, a 2-year lagged analysis was performed and an increased risk of PD was also demonstrated. In addition, the relative risk of PD was 1.7 times greater among users of anxiolytics during follow-up, compared to nonusers.

Ascertainment of the predictive power of such traits and psychiatric signs and symptoms in prospective longitudinal studies of individuals without PD is essential and is ongoing, through several of the at-risk cohorts being studied.[4]

Cognitive Dysfunction

In the HAAS cohort, 3,456 men 71 to 93 years of age without PD or dementia were administered the cognitive abilities screening instrument and followed until PD diagnosis or for 8 years. The total score on this test was not associated with

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TABLE 2 Potential clinical features and objective markers of premotor PD

Marker category	Marker	Potential predictive value
Clinical	Olfactory dysfunction[5–8]	In men, relative odds of 5.2 for the development of PD among those scoring in the lowest quartile of odor identification[8] Five-year risk of developing PD among first-degree relatives of PD patients with unexplained olfactory deficits estimated at 12.5%[7]
	RBD[9]	Cumulative risk of developing a diagnosable neurodegenerative syndrome: 33.1% at 5 years and 90.4% at 14 years[9]
	Excessive daytime sleepiness[10]	Odds of developing PD 3.3 times in those with excessive daytime sleepiness, compared to those without[10]
	RLS[11]	Limited data; compared to those without severe RLS, relative risk of developing PD was 2.77 among men with reported severe RLS symptoms (among those in whom PD was diagnosed within 4 years of RLS diagnosis)[11]
	Cognitive abnormalities[12]	Limited data; age- and education-adjusted incidence of PD 10.9 per 10,000 person-years among those in the highest quartile on executive function subscale score, compared to 26.1 for those in the lowest quartile[12]
	Constipation[13]	Age-adjusted PD incidence 3.9 per 10,000 person-years in men with reported >2 bowel movements/day and 18.9 in men with <1 bowel movement/day[13]
	Specific personality traits[14]	Limited data
	Depression[15,16]	PD patients 2.4[15] to 3.24[16] times the odds of having history of depression, compared to controls
	Anxiety[17]	Limited data; relative risk of PD 1.7 times greater among users of anxiolytics, compared to nonusers[17]
Imaging	Striatal dopamine deficiency (SPECT)[18]	Present in all hyposmic first-degree relatives of PD patients who developed PD[6] and 75% of RBD patients who developed PD[18]
	PD-related covariance pattern (PET and SPECT)[19]	Limited data; present on SPECT in all RBD patients who converted to PD and in 3 of 9 who did not convert to PD[19]
	SN hyperechogenicity transcranial Doppler sonography[20]	17-fold increased relative risk for developing PD among those with TCS SN hyperechogenicity[20]
	Hippocampal hyperperfusion on SPECT[21]	Limited data; increased hippocampal mean regional cerebral blood flow present in 10 RBD patients who developed a neurodegenerative parkinsonian syndrome, compared to 10 who did not[21]
Electrophysiological	Severity of REM atonia loss[22] (EEG slowing predicts emergence of MCI, but has not yet been shown to predict parkinsonism)[23,24]	Limited data; tonic surface EMG activity on submental EMG greater among the 12 RBD patients who developed PD, compared to 13 who developed dementia (DLB or AD)[22]
Other	Reduced color discrimination[25]	Limited data; 74% of 64 RBD patients with impaired color vision developed neurodegenerative disease (16 dementia and parkinsonism, 4 idiopathic PD) over 5 years, compared to 30% of those with normal color vision[25]

increased risk of incident PD. However age- and education-adjusted incidence of PD was 10.9 per 10,000 person-years among those in the highest quartile on the executive function subscale score, compared to 26.1 for those in the lowest quartile.[12] Whether a specific pattern of cognitive dysfunction is part of the premotor syndrome remains to be confirmed in additional studies. In line with the HAAS study, preliminary findings from the Parkinson's At-Risk Study suggest that cognitive dysfunction is associated with striatal dopaminergic deficit.[36] As we learn more about the cognitive status of premotor PD individuals, assessment of the utility of cerebrospinal fluid (CSF) and blood-based markers associated with cognitive dysfunction in PD, such as CSF β-amyloid[37] and serum epidermal growth factor,[38] respectively, will be important as well.

Sleep Disorders and Daytime Sleepiness

Rapid Eye Movement Sleep Behavior Disorder

Rapid Eye Movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by loss of the atonia that normally occurs during REM sleep, associated with dream enactment behavior. In a small subset of patients, RBD may be secondary to identifiable causes (present at the time of RBD diagnosis), such as focal brainstem lesions or narcolepsy. However, in the vast majority of so-called idiopathic RBD (iRBD) cases, there is no evidence for a diagnosable neurological disorder at the time of RBD diagnosis, but a neurodegenerative disorder emerges, usually within a few years, but sometimes decades, after onset. In fact, use of the term iRBD may be a misnomer in most cases, because neurodegeneration is likely the underlying cause of most cases of RBD, but will be the term used in this review, to maintain consistency with the current literature.

By far, the most common proteinopathy eventually diagnosed in individuals with RBD is a synucleinopathy. In the largest prospective series, 174 RBD cases were followed for a median of 4 years (range, 0.1–15.0).[9] Median age at RBD diagnosis was 69 years (approximately 5 years after onset of dream enactment), and median age at last follow-up was 74. At last follow-up, 65 (37.4%) patients were diagnosed with a defined neurodegenerative syndrome, with dementia with Lewy bodies (DLB) in 29 cases, PD in 22, mild cognitive impairment (MCI) in 12, and MSA in 2. The cumulative risk of developing a

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diagnosable neurodegenerative syndrome was 33.1% at 5 years and 90.4% at 14 years. Similarly, among 172 cases with neuropathological diagnoses, the underlying pathology was a synucleinopathy in 94% of the patients with clinical history of RBD.[39] Other less-common pathologies include AD and the SCAs. Tauopathies (such as PSP, corticobasal ganglionic degeneration, and frontotemporal degeneration associated with microtubule-associated protein tau mutation) are distinctly rare among individuals with polysomnographically confirmed RBD. In fact, presence of dream enactment in a patient with presumed tauopathy, such as PSP, should prompt evaluation for RBD mimickers, such as obstructive sleep apnea.[40,41]

RBD is postulated to result from dysfunction in brainstem nuclei, including the glutamateric perilocus coeruleus, combined with abnormalities in brainstem locomotor centers.[42] Progression from iRBD to a clinically diagnosable synucleinopathy, often with associated cognitive impairment, is in keeping with Braak's proposed neuropathological staging system[43]: Isolated RBD is present at a time when only brainstem nuclei would be involved in the pathological process (Braak stage 2), and motor and cognitive symptoms (stages 3 and 4) emerge as the pathology spreads.

As described above, there is robust evidence that the vast majority of cases of so-called iRBD will go on to develop a synucleinopathy, usually within a few years of diagnosis.[9] However, as also mentioned, there is a minority of patients in which this does not occur, and in others, this may not occur for decades after onset of dream enactment. Thereby comes the need for biomarkers to help identify which RBD patients will progress to a clinically diagnosable neurodegenerative disorder and when. In the future, such biomarkers (Table 2) will be used to gauge risk, the time course for such risk, which synucleinopathy is most likely to emerge, and, hopefully, which disease-modifying agent is most appropriate, as these agents emerge.

Restless Legs Syndrome

Restless legs syndrome (RLS) is a disorder characterized by uncomfortable sensations in the limbs, occurring in the evening or at night, and associated with an urge to move the limbs. In the HPFS, 22,999 men without PD were assessed for RLS symptoms and followed up for up to 8 years, during which 200 incident cases of PD were identified.[11] The relative risk of developing PD was increased among men who reported RLS symptoms that occurred more than 15 times per month, compared to those without, but this was statistically significant only for PD cases diagnosed within 4 years of RLS diagnosis (relative risk of 2.77).[11] These findings suggest that incorporation of RLS in to the premotor PD syndrome may be warranted if these findings are confirmed in other studies.

Excessive Daytime Sleepiness

In the HAAS,[10] 3,078 men, 71 to 93 years of age, were assessed for excessive daytime sleepiness (EDS) by a researcher-administered questionnaire. EDS was present in 244 (7.9%) cases. During follow-up, 43 of the 3,078 men developed PD. The odds of developing PD was 3.3 times higher in those with EDS, as compared to those without. Adjusting for age, baseline depression, cognition, caffeine intake, and other potential confounders did not appreciably alter the association. Of note, report of daytime napping, insomnia, and frequent nocturnal awakening was not associated with increased risk of PD.[10]

Gastrointestinal and Autonomic Dysfunction

Constipation

In the HAAS,[13] bowel movement frequency was assessed in 6,790 men. Over 24 years of follow-up, 96 men developed PD. Age-adjusted PD incidence increased significantly with decreasing bowel movement frequencies per day, from 3.9 per 10,000 person-years in men with more than 2 bowel movements per day to 18.9 in men with <1 bowel movement per day, and the relationship persisted after adjustment for covariates. In the HAAS, the association between constipation and the neuropathological finding of incidental Lewy bodies (ILB) was also examined.[12] Among those with more than 1 bowel movement per day, the age-adjusted percentage of brains with ILB was 13.5%, compared to 24.1% in those with less than 1 bowel movement per day. This was seen as evidence that constipation may be one of the earliest markers of the pathological processes underlying PD.[12] Consistent with the clinical observation that constipation precedes PD diagnosis by years, alpha-synuclein (α-Syn) has been detected in gastrointestinal tract biopsies taken from patients years preceding their PD diagnosis.[44,45]

Other Autonomic Symptoms

Occurrence of autonomic symptoms in iRBD patients provides evidence that autonomic dysfunction is part of the premotor PD syndrome. Postuma et al.[46] assessed 91 iRBD patients for autonomic symptoms with structured clinical interview and orthostatic blood pressure measurements. They followed them longitudinally for an average duration of 3.3 ± 2.3 years. Thirty-two developed a parkinsonian disorder (17 PD, 11 possible DLB). Autonomic findings were compared between these 32 patients and the RBD patients who did not have evidence of a parkinsonian disorder at last follow-up, as well as with age- and gender-matched controls. Those who developed a parkinsonian disorder were more likely to have orthostatic drops in systolic blood pressure (13.8 mm Hg greater, compared to those who did not develop a disorder and 20 mm Hg greater, compared to controls), urinary dysfunction, and constipation. Erectile dysfunction (ED) was more common, compared to controls. Onset of autonomic dysfunction in relation to diagnosis of parkinsonian disorder was estimated at 20.4 years for orthostatic declines in systolic blood pressure, 15.3 years for constipation, 13.3 years for urinary dysfunction, and 11.2 years for ED. Of note, among patients with RBD who had not (yet)

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developed a parkinsonian disorder, autonomic abnormalities were present and were intermediate in severity between those who did develop a parkinsonian disorder and controls.[46]

Objective Measures of Autonomic Function

Although evidence to support the inclusion of autonomic symptoms in the preclinical syndrome of PD exists, as detailed above, data on objective measures of dysautonomia (aside from orthostatic blood pressure measurements) are less robust, but certainly warrant further study. Two such measures include cardiac [^{123}I]-metaiodobenzylguanidine (MIBG) SPECT scans and heart rate variability analysis. Uptake of [^{123}I]-MIBG on cardiac SPECT imaging reflects cardiac postganglionic sympathetic innervation and is reduced in patients with early PD.[47,48] Whether cardiac MIBG scan is useful in detecting preclinical PD remains to be seen from longitudinal studies, but cardiac MIBG scan abnormalities in iRBD patients suggests that this is a possibility.[49] Heart rate variability is a normal occurrence during sleep and is reduced in PD as well as in individuals with iRBD.[50] However, this is yet to be demonstrated to predict emergence of motor PD.[51]

Multimodal Prediction: Importance of Imaging and Other Objective Biomarkers

As detailed above, a variety of nonmotor symptoms may be part of the premotor PD phase. However, many nonmotor features, such as hyposmia and constipation, are relatively nonspecific, particularly in older adults, and their positive predictive value for occurrence of PD is low in isolation. Thus, a two-staged approach, involving low-cost, high-sensitivity screening for preclinical symptoms and signs, followed by higher cost, high-specificity testing has been proposed. For example, olfactory function testing, followed by striatal dopaminergic imaging, has been widely advocated for.[7,52]

Multimodal assessments that incorporate not only nonmotor symptoms, but also imaging and biofluid biomarkers will be essential to not only predict which individuals will develop PD, but also when this will occur. Putative PD biofluid biomarkers that warrant investigation in premotor PD, among others, including CSF and serum DJ-1, CSF α-Syn, and serum uric acid and apolipoprotein A1.[53] Results from ongoing premotor PD cohorts that have incorporated biofluid biomarker testing, are eagerly awaited.

Various imaging modalities have already been investigated as biomarkers for the premotor phase, with interesting and promising results.[54] Many of the modalities discussed below have also been applied to individuals with preclinical PD, such as asymptomatic individuals carrying mutations known to be associated with PD.[55,56] Though these studies are beyond the scope of this review, suffice to say these imaging markers are of particular interest in these presymptomatic carriers, where the variable clinical penetrance of these mutations makes ancillary information predictive of future risk of PD essential, and where intervention would hypothetically be the most likely to meaningfully reduce risk of PD emergence.

Dopaminergic Imaging

The nigrostriatal dopaminergic system can be imaged *in vivo* using both PET and SPECT; radioligands for the dopamine transporter are commercially available, and radioligands to various other presynaptic and postsynaptic targets are being developed. The rationale for incorporation of dopaminergic system imaging into preclinical and -motor PD characterization is based on estimates that that the onset of dopaminergic neuronal loss antedates the clinical diagnosis of PD by approximately 4 to 6 years[57,58] and, in PD, progresses at a rate of approximately 11% per year, though this does not correlate with clinical progression.[59] As mentioned above, several cohorts have been assembled to better define the premotor PD phases,[4] and many have incorporated dopaminergic imaging. Longitudinal data are eagerly awaited.

Application of dopaminergic imaging to the premotor PD phase is exemplified in its use to predict emergence of PD in those with iRBD. Iranzo et al.[18] studied a cohort of 43 individuals with iRBD, with a mean RBD disease duration of 9.4 years and a mean follow-up duration of 3.54 years. Seventeen (40%) had reduced striatal binding on DAT-SPECT.[18] Eight individuals (30% of those with reduced striatal binding) developed a neurodegenerative parkinsonian syndrome (5 PD, 2 DLB, and 2 MSA); all but 2 of those with normal dopaminergic imaging remained disease free.[18] Of note, this cohort was also assessed with transcranial sonography (TCS), as detailed further below.

Despite the promise held in dopaminergic imaging, it has limitations, including cost and logistical challenges. Importantly, if, as hypothesized by Braak,[43] neurodegeneration begins in extranigral regions first, imaging to assess pathology of dopaminergic outside of the nigrostriatal system (as well as and nondopaminergic neurons) is ultimately essential as well.

TCS

An enlarged area of SN hyperechogenicity on TCS is strongly associated with PD, occurring in over 90% of PD patients, compared to 10% of healthy older adults,[60] and is present even in early stages.[61] Data suggest that TCS may also be useful in characterization of preclinical PD. In the Prospective Validation of Risk Factors for the Development of Parkinsonian Syndrome (PRIPS) study,[20] 1,847 individuals over the age of 50 underwent TCS and were followed for 3 years. Eleven developed PD. An enlarged area of SN hyperechogenicity was present in 80% of those that developed PD on follow-up, compared to 18.3% of those who did not. There was a 17-fold increased for developing PD among those with this TCS finding.[20]

TCS was also been applied by Iranzo et al.[18] in iRBD, along with DAT-SPECT (discussed above). Of 39 individuals with iRBD who had TCS, SN hyperechogenicity was present in 14 (36%). Five went on to develop a neurodegenerative parkinsonian syndrome; 2 of those had normal striatal binding on DAT-

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SPECT. The combination of TCS and DAT-SPECT had 100% sensitivity for prediction of conversion to a neurodegenerative parkinsonian syndrome and a specificity of 55%.[18] This study is a good example of combining clinical and multimodal imaging biomarkers for characterization of the premotor PD syndrome. Of course, the low specificity may relate to the relatively brief duration of follow-up, and it is expected that, on longer follow-up, a greater number of cases with imaging abnormalities will develop a neurodegenerative parkinsonian syndrome. Biomarkers that detect risk with a longer lead time are clearly needed. In addition, limitations of TCS are important considerations, including establishing cut-off values for defining the SN, inability to identify a bone window (in the skull, through which to perform the study) in a subset of patients, and technical and logistical requirements, including need for specialized operator training and ultrasonography expertise.

Electrophysiological Measures

As mentioned above, idiopathic RBD is associated with the polysomnographic finding of REM sleep without atonia (RSWA), whereby the atonia normally present during REM sleep is replaced with intermittent (phasic) or sustained (tonic) muscle activity as can be detected and quantitated using surface electromyography (EMG) electrodes. The severity of RSWA has been associated with PD severity[62,63]. The severity of RSWA has also been shown, in one study, to predict the emergence of PD. Twenty-six patients underwent a polysomnogram 6.7 years before disease onset. Those who developed PD had increased tonic EMG activity during REM sleep in the mentalis, compared to those who remained disease free or those who developed dementia.[22]

EEG slowing, as assessed with quantitative EEG techniques, has been found in iRBD [23] and predicts the diagnosis of MCI.[24] EEG changes that predict emergence of a neurodegenerative parkinsonian syndrome have yet to be reported, but this deserves further study.

Conclusion

There is optimism that, in coming years, disease-modifying therapies will emerge for PD and other neurodegenerative parkinsonian syndromes. With this promise comes the need to improve both our diagnostic accuracy and our ability to detect these disorders much earlier in their course. To that end, a redefinition of PD into preclinical, premotor, and motor phases has been proposed and will likely facilitate research in this area. Characterization of preclinical and premotor phases, both clinically and with objective measures, is essential. The field has made remarkable advances on both of these fronts. Though some studies have been prospective, much of the data to date come from retrospective and case-control studies. In the past decade, there has been intensive effort to establish cohorts of individuals potentially at risk for PD, for prospective assessment. Several large cohorts have been assembled and crucial studies are now under way; their results are eagerly awaited.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

L.M.C.: 1A, 1B, 1C, 3A, 3B

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