Diagnosis and the premotor phase of Parkinson disease

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ABSTRACT

Clinical, neuroimaging, and pathologic studies have provided data suggesting that a variety of nonmotor symptoms can precede the classic motor features of Parkinson disease (PD) by years and, perhaps, even decades. The period when these symptoms arise can be referred to as the "premotor phase" of the disease. Here, we review the evidence supporting the occurrence of olfactory dysfunction, dysautonomia, and mood and sleep disorders, in this premotor phase of PD. These symptoms are well known in established PD and when presenting early, in the premotor phase, should be potentially considered as an integral part of the disease process. Even though information on the premotor phase of PD is rapidly accumulating, the diagnosis of premotor PD remains elusive at this time. Should a safe and effective treatment with disease-modifying or neuroprotective potential in PD become available, identifying individuals in the premotor phase will become a serious priority. **NEUROLOGY 2009;72(Suppl 2):S12–S20**

The clinical diagnosis of Parkinson disease (PD) is based on the identification of a combination of the cardinal motor signs of bradykinesia, rest tremor, and rigidity. A favorable response to levodopa or dopaminergic agonists is also considered important for a reliable diagnosis. When diagnosis is made using these criteria, it is accepted that extensive loss of dopaminergic neurons in the substantia nigra (SN) and a significant reduction of striatal dopamine content, have taken place.[1–5]

Early diagnosis of PD is desirable to provide appropriate management and adequate prognosis. Furthermore, recent studies (e.g., TEMPO and ELLDOPA) suggest that early treatment may provide a better outcome than a delayed one.[6,7] Efforts have been directed to diagnose PD in the very early stages—e.g., when motor signs are inconclusive or "soft" and the response of these symptoms to dopaminergic treatment is unknown—since, in these early stages, it is presumed that neural damage is more restricted. Recently, efforts in diagnosis have been extended to even earlier in the disease course. Clinical, neuroimaging, and pathologic studies have provided data suggesting that a variety of nonmotor symptoms can precede the classic motor features of PD by years and, perhaps, even decades.[8–12] The period when these symptoms arise can be referred to as the premotor phase of the disease. The recent proposal by Braak et al.[13] that synuclein pathology (Lewy bodies and neurites) in PD starts in the lower brainstem and progresses following a predictable caudal-rostral pattern, only reaching the SN in the mesencephalon after extensive involvement of the brainstem has occurred, lends support to the notion that nonmotor features reflecting this "prenigral" involvement can antedate the classic motor features of PD.

The recognition that nonmotor symptoms occur in the premotor phase has revolutionized our understanding of PD, and opened up the possibility of an early presymptomatic diagnosis. Furthermore, it has changed the way we assess patients in whom we suspect a diagnosis of PD. Until recently, a neurologist would not have spent so much time on patients presenting with, for example, finger tremor, inquiring about olfaction, perspiration, sleep, and bladder or bowel functions, and the expertise of neurologists in these areas is increasing. It has also prompted the shifting of a large amount of research effort toward identification of subjects at risk of the development of the motor signs of PD, before degeneration of dopaminergic neurons in the SN has occurred.

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Table Nonmotor symptoms in the premotor phase of PD and their neuropathological substrates

Nonmotor symptoms in PD	Presumed underlying brain structures	Nonmotor symptoms well documented in the premotor phase	Corresponding Braak stage
Olfactory loss: impairments in odor detection, identification and discrimination	Olfactory bulb; anterior olfactory nucleus; amygdala; perirhinal cortex	Hyposmia	1 Olfactory bulb and anterior olfactory nucleus
Dysautonomia			1
Gastrointestinal disturbances: gastroparesis, constipation Urinary dysfunction: urinary frequency and urgency, nocturia Sexual dysfunction: men – impaired erection and ejaculation dysfunction; women – impaired vaginal lubrication, problems in reaching orgasm Orthostatic hypotension	Amygdala; dorsal nucleus of the vagus; intermediolateral column of the spinal cord; sympathetic ganglia; enteric and abdominopelvic autonomic plexuses	Constipation; genito-urinary dysfunction	Dorsal nucleus of the vagus (sympathetic ganglia; enteric and abdominopelvic autonomic plexuses?)
Mood disorders (behavioral/emotional dysfunction): depression, anxiety	Locus coeruleus; raphe nuclei; amygdala; mesolimbic, mesocortical cortex	Depression; anxiety	2–3 Locus coeruleus; raphe nuclei
Sleep disturbances: REM behavior disorder, excessive daytime sleepiness, insomnia	Nucleus subcoeruleus; pedunculopontine nucleus; thalamus; hypothalamus	REM behavior disorder; excessive daytime sleepiness	2 Nucleus subcoeruleus; pedunculopontine nucleus
Other nonmotor symptoms: pain, apathy, fatigue, mid-life obesity, impaired color discrimination, restless legs syndrome, rhinorrhea	Unclear	Unknown	Unclear
Hallucinations, psychosis	Amygdala; limbic cortex	?*	4–5
Cognitive dysfunction and dementia	Frontal and ventral temporal lobe/neocortex; hippocampus; amygdala; nucleus basalis of Meynert; locus coeruleus	?*	5–6

*Hallucinations, psychosis and dementia can be considered as possible premotor manifestations of PD. When occurring before parkinsonism (premotor), they are regarded, arbitrarily, as the early manifestation of dementia with Lewy bodies and not as a premotor manifestation of PD.

The text that follows reviews the evidence supporting the occurrence of olfactory dysfunction, dysautonomia, and mood and sleep disorders in the premotor phase of PD. These symptoms are well known in established PD and when presenting early, in the premotor phase, should be considered, at least in some instances, as an integral part of the disease process (table).

Olfactory loss in premotor PD. Olfactory loss (hyposmia) occurs in up to 90% of PD patients and involves several aspects including impairment of odor detection, identification, and discrimination.[14] Olfactory deficits seem to be independent of disease severity and duration, since they can be detected in untreated, newly diagnosed PD patients. In addition, olfactory loss occurs bilaterally, even when motor signs are asymmetrical or unilateral.[15–17] These observations, and a notable number of subsequent studies, have led to olfactory loss being considered as a premotor symptom of PD.

An association between impaired olfaction and the future development of PD was found in a population-based prospective study.[18] In this study, olfaction was assessed in 2,267 elderly subjects without PD and dementia who were included in the Honolulu Heart Program. After 8 years of follow-up, 35 subjects had subsequently developed PD. Subjects with a higher risk for developing PD were those who presented an odor identification score in the lower quartile. Interestingly, the risk for developing PD in the subjects in the lower quartile was significantly increased within the first 4 years, whereas for the second 4 years of follow-up, there was no apparent relationship between olfactory loss at baseline and the incidence of PD. These results suggest that olfactory loss can predate the development of clinical PD by up to 4 years.[18] In this population, 164 subjects who later died without being diagnosed with PD in the study follow-up, underwent postmortem examination. Incidental Lewy bodies in the SN and the locus

coeruleus were observed in 17 subjects, who had a mean odor detection score that was significantly lower than subjects without incidental Lewy bodies at autopsy.[11]

In another study, 30 patients with idiopathic hyposmia were examined by transcranial sonography to evaluate the presence of increased SN echogenicity, which is thought to be a susceptibility marker for PD.[19] Eleven patients showed SN hyperechogenicity and, in five of these 11 patients, dopamine transporter (DAT) SPECT disclosed altered striatal tracer uptake.[19] It is noteworthy that one of these patients had subtle parkinsonian signs at the moment of study. Four years later, two subjects had subtle parkinsonian signs, and two subjects had developed definite PD.[12] Other studies have also shown that hyposmia is frequently present in patients with REM sleep behavior disorder (RBD), a sleep disorder that is also well established as a premotor symptom of PD (see later in this review).[20,21]

Olfactory dysfunction has also been observed in some asymptomatic relatives of patients with either familial or sporadic forms of PD.[22–26] A study examining olfactory function in 250 relatives of PD patients identified 25 hyposmic relatives who subsequently underwent DAT SPECT imaging.[24] Abnormal reduction in striatal dopamine transporter binding was observed in four out of these 25 hyposmic relatives, two of whom subsequently developed clinical parkinsonism 6 to 12 months after the DAT SPECT study.[24] As a consequence of these results, a follow-up study was conducted in an extended cohort of first-degree relatives of patients with PD. Sense of smell was analyzed in 361 asymptomatic relatives of patients with PD, and 40 hyposmic relatives were identified. Within 2 years of follow-up, 10% of this subgroup had developed PD and another 12% had detectable presynaptic abnormalities on their DAT SPECT scan, in contrast to none of the normosmic relatives of the cohort.[25]

In a study of 62 twin pairs discordant for PD, odor identification ability was reduced at baseline in twins with PD, whereas hyposmia was not detected in any of the unaffected twins at baseline.[27] After a mean follow-up of 7.3 years, two initially unaffected twins developed PD. These two new PD twins presented with a greater decline in follow-up smell test scores than the remaining 17 unaffected twins. The authors concluded that hyposmia is not present more than 7 years before the onset of the motor symptoms of PD.

All these studies strongly suggest that olfactory loss is an early feature of PD, which develops before parkinsonian motor signs are detectable. Olfactory testing is easy to perform and, therefore, is likely to have a role as a biomarker in future strategies aimed at detecting subjects at risk for developing PD or who are in the premotor phase of the disease. However, it has not yet been demonstrated that hyposmia unequivocally precedes neuronal loss in the SN, as would be expected on the basis of Braak staging. The available data from the studies reported here suggest that olfactory loss starts between 2 and 7 years before PD diagnosis and, similarly, imaging studies of the dopaminergic system and postmortem cell counts of pigmented neurons in the SN, suggest periods between the onset of neuronal loss in the SN and PD diagnosis of approximately 4 to 6 years.[3–5] Whether hyposmia precedes, or occurs simultaneously with neuronal loss of the SN still requires clarification.

Dysautonomia in premotor PD. Some autonomic disturbances are frequently observed in PD at the time of diagnosis,[28] and have been found to precede the onset of motor symptoms.[29,30] Consequently, they are often considered as premotor symptoms or risk factors for further development of the cardinal motor symptoms and signs of PD.[31–34]

Gastrointestinal motility problems such as regurgitation, nausea, and epigastric discomfort, which are all likely to be related to gastroparesis, have been said to predate motor symptoms in some cases of PD.[35–38] However, constipation is the autonomic disturbance with the strongest and most consistent evidence for being one of the so-called premotor PD symptoms.[29,39,40] In recent years, studies have shown that autonomic disturbances such as urinary or erectile dysfunction, could also occur in the premotor phase of PD.

Constipation is present in up to 60–80% of patients with PD,[40–43] and is also common in patients with PD of recent onset.[44,45] It is not infrequent that patients with PD report a long-lasting history of constipation years before the onset of motor symptoms. A study of constipation symptoms and colorectal function in 12 patients with PD, found that constipation antedated the development of parkinsonian symptoms by an average of 10 years or longer in 10 of the 12 patients.[41] In a case-control study assessing bowel movements and nutritional status in 94 patients with PD, onset of constipation occurred before the onset of motor symptoms in 33 of 74 patients with constipation (44.6%).[39] In this study, constipation preceded the motor symptoms of PD by an average of 18 years.

In contrast, another case-control study assessing premotor complaints of patients with PD from a national general practitioners' records system, found that diarrhea, but not constipation, was reported more frequently among patients with PD than controls.[8] The authors considered the diarrhea as a possible compensatory mechanism in the setting of very incipient autonomic dysfunction. A recent study of

pathologically confirmed PD cases where premotor complaints were assessed, did not mention premotor constipation or any other gastrointestinal symptom, although the retrospective design of such a clinicopathologic study could account for the surprising lack of gastrointestinal complaints in the series.[46]

A clear demonstration that constipation can precede PD has come from a large population-based prospective epidemiologic study in elderly subjects without PD and dementia included in the Honolulu Heart Program.[29] The study found a 2.7-fold risk of PD among men with less than one bowel movement/day vs men with one or more bowel movements/day. The risk of PD in men with less than one bowel movement/day further increased to 4.1 when compared with men with more than two bowel movements/day. In this study, constipation seemed to be associated with an earlier age at onset of PD, although these findings could have been related to the fact that the frequency of constipation increases in the elderly.[29] In an extension of this study, 245 subjects who died without being diagnosed with PD or dementia during their lifetimes, had a postmortem study, and incidental Lewy bodies were identified in 30 subjects (12.2%).[47] The subjects in whom incidental Lewy bodies were detected had a greater decrease in bowel movement frequency during their lives than subjects without Lewy bodies,[47] providing further evidence that constipation can predate motor symptoms. Whether constipation was related to the underlying pathophysiological processes of PD and, as such, was a sign of early PD, or was a risk factor linked to other susceptibility or environmental factors for PD, could not be determined in these studies. However, recent pathologic studies showing that α-synuclein deposition may take place at the dorsal nucleus of the vagus and, even more distally, at the enteric plexus,[13,48] before involvement of the SN, favor the notion of constipation as a premotor symptom of PD.

Genitourinary disturbances and erectile dysfunction have also been proposed as premotor symptoms of PD, although clear evidence from prospective studies such as those available for constipation or other premotor symptoms, e.g., hyposmia, is lacking. Some patients with PD, when asked specifically, confirm that sexual dysfunction has preceded the onset of motor symptoms,[49] and a recently published retrospective analysis of a large cohort of men from the Health Professionals Follow-up Study followed up between 1986 and 2002, has shown a 3.8-fold increase in the likelihood of developing PD among men with erectile dysfunction at baseline, the risk being even higher for younger men.[30] A clinicopathologic survey of 433 pathologically confirmed PD cases, found that urinary dysfunction was among the commonest nonmotor presenting complaints in PD.[46] A case of PD presenting with symptoms of bladder dysfunction 1 year before the development of classic motor signs and, consequently, misdiagnosed at first as multiple system atrophy, has recently been reported, showing Lewy body-type pathology involving Onuf's nucleus as the putative substrate of this dysautonomic presentation.[50]

In support of gastrointestinal and genitourinary symptoms occurring early in PD are findings showing that 9% to 17% of subjects without a clinical history of PD had synuclein aggregates in the peripheral autonomic nervous system, including abdominopelvic autonomic plexuses, the myenteric plexus of the esophagus, the sympathetic ganglia and the vagus nerve,[51,52] with some patients showing incidental Lewy body pathology on neuropathological examination.

Complaints related to the cardiovascular system, mostly those derived from postprandial and orthostatic hypotension (OH), are uncommon in early PD. Nevertheless, the vulnerability of the autonomic system to synuclein pathology suggests that involvement of autonomic cardiac structures could occur in early phases of development, and recent clinical, cardiac imaging and neuropathological studies, have focused attention on the cardiovascular system in premotor PD.[53,54] One study found that OH, defined as a drop of more than 20 mm Hg in systolic pressure and 5 mm Hg in diastolic pressure from lying to standing, had preceded parkinsonism in four of 35 patients with both PD and OH.[53] Another study of the prodromal phase of PD did not detect OH or an increase in the number of visits to cardiologists, but unexpectedly detected a higher incidence of hypertension in PD patients compared with controls.[8] The authors regarded such a paradoxical feature as a compensatory mechanism in the setting of incipient dysautonomia. In recent years, the study of heart sympathetic innervation using nuclear medicine techniques such as SPECT with metaiodobenzylguanidine (MIBG) has led to observations that cardiac uptake can be reduced in the very early stages of PD, indicating early cardiac sympathetic denervation.[55] Decreased immunostaining for epicardial tyrosine hydroxylase has been found in individuals with incidental Lewy bodies,[56] and there is growing evidence that synuclein aggregates in the distal axons of the cardiac sympathetic nervous system heralds centripetal degeneration of the cardiac sympathetic nerve in PD.[54] The functional consequences of early cardiovascular involvement in the pathologic process are unclear, as no relationship has been found between cardiovascular symptoms and neurophysiological measures of sympathetic failure or cardiac uptake

MIBG SPECT.[57,58]

Mood disorders in premotor PD. Depression is common in PD. Prevalence rates of depression in patients with PD reported in the literature vary widely, ranging from 2.7% to 90%, probably depending on the nature of the population studied, and the criteria used for depression diagnosis. A recent systematic review of the different studies assessing the prevalence of depressive syndromes in PD, found an average prevalence of major depressive disorder in PD of 17%, while minor depression was present in 22% and dysthymia in 13% of PD patients.[59] There are several lines of evidence supporting the concept that depression in PD probably has a biologic rather than a pure psychological reactive basis.[60] In fact, prevalence of depression in PD is higher than in patients suffering from other disabling disorders, and the correlation between depression and disease duration and severity is weak. In addition, depressive symptoms in PD are characterized by the relative absence of guilt, shame, or sorrow, when compared with depression in the general population.[60–62]

Depression can occur in up to 27.6% of patients with PD in the early stages of the disease,[63] and several studies have revealed that depressive symptoms can precede the development of motor manifestations.[8,64–71] Approximately 20% of patients with PD complain of depressive symptoms years before the onset of motor signs.[61,64] Development of depression can predate PD diagnosis by up to 20 years, but its incidence shows a particular rise during the 3- to 6-year period before diagnosis.[64,65,69] Several studies have also shown that depressed patients have a 2.2- to 3.2-fold higher risk for developing PD than nondepressed subjects.[66,67,69] A recent study using transcranial sonography found that marked SN hyperechogenicity, which is thought to be a susceptibility marker for PD, was 3-fold more frequent in depressed non-parkinsonian patients than in the age-matched normal population, which is congruent with the aforementioned risk of 2.2 to 3.2 for depressed patients developing PD.[72]

These findings support the view that depression can be an early premotor manifestation of PD. However, robust evidence for premotor depression, provided by prospective studies such as those available in hyposmia, is still lacking. In addition, no information is available on whether premotor PD-related depression differs from primary depression in its essential clinical features and response to treatment. Anxiety, apathy, and fatigue, which are nonmotor symptoms that could be related to depression, and that are frequently observed in established PD, have also been proposed as premotor symptoms, although strong evidence for this is still lacking.[33,65]

Sleep disturbances in premotor PD. Sleep disturbances are 1.5 to 3.5 times more common in established PD than in healthy controls or patients with other chronic disorders[73–77] but, in the early phases of the disease, sleep disorders are relatively uncommon.[77–79] Only when the disease advances do sleep disturbances become clinically significant because of a combination of factors. There are exceptions to this rule, however. One is RBD, a parasomnia that may precede the diurnal motor symptoms of PD by several years, as it has been found in retrospective case reports and series[80,81] and, more recently, in a descriptive study with long-term follow-up.[10] Abnormal sleep may also be an early feature in some forms of familial parkinsonism.[82] Another exception may be excessive daytime sleepiness (EDS) which, at least in one large epidemiologic study in healthy elderly men,[83] was found to be more frequent in those individuals who later developed PD than in those who did not.

RBD consists of recurrent episodes of sudden, abnormally vigorous body, head or limb movements that appear during REM sleep, often associated with dreams in which the patient defends against a threat or aggression. In its most severe form, patients may injure themselves or their bed partner but, in milder forms of RBD, patients may not be aware of the parasomnia, particularly if they sleep alone.[81] RBD occurs in at least 30% of patients with PD,[84] but this figure is probably conservative because patients with cognitive changes and those treated with antidepressants or hypnotics were excluded. In about 20% of PD patients with RBD, the reported onset of RBD antedates that of parkinsonism by several years.[85] Even though idiopathic RBD can evolve into diseases other than PD, RBD has to be considered a premotor symptom, at least in some PD patients. This sequence of events—that is, RBD antedating the classic motor signs—may be expected to occur regularly in PD, since brainstem structures such as the subceruleus and pedunculopontine nuclei, which are thought to be responsible for RBD in PD, become involved in the neuropathological process before the SN.[13] The reason why RBD precedes parkinsonism in some, but not all, cases is unclear. In a series of 61 PD patients with RBD, parasomnia only preceded PD when parkinsonism appeared after the age of 50 years, and was much less common in patients with prominent tremor.[86] The presence of RBD in patients with PD may represent a risk factor for the development of cognitive deterioration and possibly dementia.[87]

One report described a family harboring a novel mutation in the α-synuclein gene (E46K) that segregated with a phenotype of parkinsonism or dementia

with Lewy bodies.[82] Two affected members presented with abnormal sleep behaviors suggestive of RBD, several years before parkinsonism. When studied in the sleep laboratory several years later, however, these behaviors could not be recorded despite several sleep studies; in part because the amount of sleep was clearly reduced (to less than 30% of the recording time), and also because REM sleep was not recorded. In less affected patients or in asymptomatic carriers, sleep efficiency was reduced and, in one case, excessive electromyography activity during REM sleep (suggestive of RBD) was present.

EDS has been under-recognized in PD and, although initially considered as a side effect of nonergot dopamine D_2-D_3 agonists,[88] it is not restricted to a specific class of dopaminomimetic agents, and may have other causes. One study found no increase in the prevalence of EDS in untreated PD patients compared with an age-matched healthy control group, whereas EDS was more frequent in treated patients, suggesting that either the progression of the disease, the treatment, or a combination of both, may be critical in the development of this symptom.[77] Another study found that progression of the disease by itself, before initiation of dopaminergic treatment, was associated with increased sleepiness.[78] This was confirmed in a study of the development of EDS over time in a group of 142 PD patients (age at entry, 73 years; Hoehn and Yahr stage, 2.9; disease duration, 8–10 years) followed up during a 4-year period.[89] The study found that the 11 patients with EDS at the beginning of the study also presented EDS at follow-up, and showed more cognitive impairment than the rest, whereas 30 patients developed EDS for the first time during the follow-up period, suggesting that EDS correlates with more advanced disease and dementia.

In a large series of asymptomatic elderly men, followed up from 1994 to 2001, EDS (defined as "being sleepy most of the day") was found to be a risk factor for PD, since its presence increased the chances of developing PD by 3-fold,[83] even when adjusting for other features such as insomnia, depression, coffee drinking, or cigarette smoking. This suggests that EDS may be another sleep disturbance that constitutes a premotor feature of PD.

DISCUSSION Nonmotor symptoms are now accepted as an integral part of the disease process in PD, if they occur once motor symptoms have developed. However, accumulating clinical and pathologic evidence suggests that nonmotor alterations frequently can occur before the classic motor signs of PD appear. The evidence is most compelling for sleep disturbances such as RBD, and for olfactory dysfunction, but evidence that depression, constipation, and genitourinary disturbances antedate the motor symptoms in PD, is also accumulating. Recent neuropathological studies supporting early lower brainstem involvement in PD and involvement of the peripheral autonomic structures such as the sympathetic cardiac plexus or the vesicoprostatic plexus antedating involvement of the CNS suggest an anatomical basis for these symptoms.

Exactly which neural structures are involved and whether synuclein deposition, cell loss, or neuronal dysfunction unrelated to α-synuclein deposition, is responsible for these premotor symptoms of PD, is still unclear. Another particularly intriguing question is how the clinical signs of the premotor phase correlate with the neuropathological changes postulated to occur in these early disease stages. If Braak's hypothesis is true, one could expect that most patients would suffer such nonmotor symptoms before developing the classic motor ones, as a consequence of pathology involving the lower brainstem, olfactory, and possibly peripheral autonomic, structures. Careful questioning of patients and available published information indicates that this is not the case in many instances. For example, in patients with PD with RBD, the symptoms of RBD occur before the development of motor symptoms in only 22% of patients,[85] and many patients do not report constipation or dysuria at the time of diagnosis of PD. No good explanation is available for the variable expression of these nonmotor symptoms in early and premotor PD. RBD, for example, occurred more frequently in patients older than 50 years and in those with an akinetic rather than a tremoric presentation.[86] This mismatch between presentation of symptoms and proposed progression of neuropathological lesions can be explained in several ways. Insufficient intensity of symptoms and a lack of sensitive tools to identify certain symptoms could explain their absence in the premotor phase. It is possible that the severity of neuronal dysfunction in the responsible nervous structures does not reach a critical threshold for the clinical expression of symptoms in some instances. It is also possible that Braak's proposed staging may not be valid in all instances of sporadic PD. A recent study evaluating 71 PD cases showed that the caudo-rostral spreading described by Braak and colleagues, did not occur in 47% of the cases.[90] It remains to be established by appropriate studies how often nonmotor symptoms antedate classic motor signs in PD, and how they evolve over time.

Even though information on the premotor phase of PD is rapidly accumulating, the diagnosis of premotor PD remains difficult, because of numerous

unresolved issues. We do not know, for example, how often premotor nonmotor symptoms occur in patients who eventually develop motor PD, and in what time sequence. Furthermore, in a given individual without classic motor signs of PD, we do not know when symptoms such as olfactory loss, RBD, or EDS represent premotor PD and when they do not. It is also not known if imaging of the dopaminergic system with PET or SPECT, transcranial Doppler, and cardiac scintigraphy with MIBG, are useful in identifying those cases with nonmotor symptoms associated with synuclein pathology, and how useful these tests are in predicting the development of motor signs. In addition, what is the risk of individuals suffering from one or several of these symptoms, developing motor PD in their lifetime? No good answers to these questions are currently available and, consequently, it remains difficult, if not impossible, to reliably diagnose PD before the development of the cardinal motor signs.

In an attempt to better define the clinical characteristics of the premotor phase of PD, appropriate studies are needed. Such studies need to centre on individuals who are at risk of developing classic PD but who are still asymptomatic for motor symptoms. As an example, abnormal olfaction has been evaluated as a possible risk factor when occurring in asymptomatic first-degree relatives of patients with PD and also in patients with idiopathic RBD. In research settings, it is now possible to identify individuals who carry genetic markers that place them at risk for PD. For example, several studies are in progress to assess the frequency and natural history of nonmotor symptoms in asymptomatic individuals with an elevated risk of developing PD because of mutations in the LRRK2 gene, and to assess the predictive value of these symptoms and of neuroimaging abnormalities, for the development of the classic motor signs.

In the future, identification of individuals in the premotor phase of PD, will allow the study of drugs with putative neuroprotective or disease-modifying properties at the very early stages of disease development, before significant neuronal loss has taken place. Should a safe and effective treatment with disease-modifying or neuroprotective potential in PD become available, identifying individuals in the premotor phase will become a serious priority. From the progress taking place in this field, it seems likely that we will soon be able to diagnose premotor PD and, consequently, meet this challenge.

REFERENCES

1. Riederer P, Wuketich S. Time course of nigrostriatal degeneration in Parkinson's disease. A detailed study of influential factors in human brain amine analysis J Neural Transm 1976;38:277–301.
2. Hornykiewicz O, Kish SJ. Biochemical pathophysiology of Parkinson's disease. Adv Neurol 1987;45:19–34.
3. Fearnley JM, Lees AJ. Ageing and Parkinson's disease: SN regional selectivity. Brain 1991;114:2283–2301.
4. Morrish PK, Rakshi JS, Bailey DL, et al. Measuring the rate of progression and estimating the premotoral period of Parkinson's disease with [18F]dopa PET. J Neurol Neurosurg Psychiatry 1998;64:314–319.
5. Marek K, Innis R, van Dyck C, et al. [123I]B-CIT SPECT imaging assessment of the rate of Parkinson's disease progression. Neurology 2001;57:2089–2094.
6. The Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. Arch Neurol 2002;59:1937–1943.
7. Fahn S, Oakes D, Shoulson I, et al. Levodopa and the progression of Parkinson's disease. N Engl J Med 2004; 351:2498–2508.
8. Gonera EG, Van't Hof M, Berger HJC, Van Weel C, Horstink MWIM. Symptoms and duration of the premotor phase in Parkinson's disease. Mov Disord 1997;12: 871–876.
9. Abbott RD, Ross GW, White LR, et al. Environmental, life-style, and physical precursors of clinical Parkinson's disease: recent findings from the Honolulu-Asia Aging Study. J Neurol 2003;250(Suppl 3):30–39.
10. Iranzo A, Molinuevo JL, Santamaría J, et al. Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. Lancet Neurol 2006;5:572–577.
11. Ross GW, Abbott RD, Petrovitch H, et al. Association of olfactory dysfunction with incidental Lewy bodies. Mov Disord 2006;21:2062–2067.
12. Haehner A, Hummel T, Hummel C, Sommer U, Junghanns S, Reichmann H. Olfactory loss may be a first sign of idiopathic Parkinson's disease. Mov Disord 2007; 22:839–842.
13. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003;24:197–211.
14. Katzenschlager R, Lees AJ. Olfaction and Parkinson's syndromes: its role in differential diagnosis. Curr Opin Neurol 2004;17:417–423.
15. Doty RL, Stern MB, Pfeiffer C, et al. Bilateral olfactory dysfunction in early stage treated and untreated idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1992; 55:138–142.
16. Stern M, Doty RL, Dotti M, et al. Olfactory function in Parkinson's disease subtypes. Neurology 1994;44:266–268.
17. Tissingh G, Berendse HW, Bergmans P, et al. Loss of olfaction in de novo and treated Parkinson's disease: possible implications for early diagnosis. Mov Disord 2001;16:41–46.
18. Ross GW, Petrovitch H, Abbott RD, et al. Association of olfactory dysfunction with risk for future Parkinson's disease. Ann Neurol 2008;63:167–173.
19. Sommer U, Hummel T, Cormann K, et al. Detection of presymptomatic Parkinson's disease: combining smell tests, transcranial sonography, and SPECT. Mov Disord 2004;19:1196–1202.
20. Stiasny-Kolster K, Doerr Y, Möller JC, et al. Combination of 'idiopathic' REM sleep behaviour disorder and olfactory dysfunction as possible indicator for alpha-synucleinopathy dem-

onstrated by dopamine transporter FP-CIT-SPECT. Brain 2005;128:126–137.
21. Postuma RB, Lang AE, Massicotte-Marquez J, Montplaisir J. Potential early markers of Parkinson disease in idiopathic REM sleep behavior disorder. Neurology 2006;66:845–851.
22. Markopoulou K, Larsen KW, Wszolek EK, et al. Olfactory dysfunction in familial parkinsonism. Neurology 1997;49:1262–1267.
23. Montgomery EB, Baker KB, Lyons K, Koller WC. Abnormal performance on the PD test battery by asymptomatic first degree relatives. Neurology 1999;52:757–762.
24. Berendse HW, Booij J, Francot GMJE, et al. Subclinical dopaminergic dysfunction in symptomatic Parkinson's disease patients' relatives with a decreased sense of smell. Ann Neurol 2001;50:34–41.
25. Ponsen MM, Stoffers D, Booij J, et al. Idiopathic hyposmia as a premotoral sign of Parkinson's disease. Ann Neurol 2004;56:173–181.
26. Siderowf A, Jennings D, Connolly J, Doty RL, Marek K, Stern MB. Risk factors for Parkinson's disease and impaired olfaction in relatives of patients with Parkinson's disease. Mov Disord 2007;22:2249–2255.
27. Marras C, Goldman S, Smith A, et al. Smell identification ability in twin pairs discordant for Parkinson's disease. Mov Disord 2005;20:687–693.
28. Awerbuch GI, Sandyk R. Autonomic functions in the early stages of Parkinson's disease. Int J Neurosci 1994;74:9–16.
29. Abbott RD, Petrovitch H, White LR, et al. Frequency of bowel movements and the future risk of Parkinson's disease. Neurology 2001;57:456–462.
30. Gao X, Chen H, Schwarzschild M, et al. Erectile function and risk of Parkinson's disease. Am J Epidemiol 2007;166:1446–1450.
31. Becker G, Müller A, Braune S, et al. Early diagnosis of Parkinson's disease. J Neurol 2002;249(Suppl 3):40–48.
32. Przuntek H, Müller T, Riederer P. Diagnostic staging of Parkinson's disease: conceptual aspects. J Neural Transm 2004;111:201–216.
33. Chaudhuri KR, Daniel G, Healy DG, Schapira AHV. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol 2006;5:235–245.
34. Tolosa E, Compta Y, Gaig C. The pre-motor phase of Parkinson disease. Parkinsonism Relat Disorders 2007;13(suppl):S2–S7.
35. Edwards LL, Pfeiffer RF, Quigley EMM, Hofman R, Baluff M. Gastrointestinal symptoms in Parkinson's disease. Mov Disord 1991;6:151–156.
36. Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. Lancet Neurol 2003;2:107–116.
37. Camilleri M, Bharucha AE. Gastrointestinal dysfunction in neurologic disease. Semin Neurol 1996;16:203–216.
38. McCallum RW, Brown RL. Diabetic and nondiabetic gastroparesis. Curr Treat Options Gastroenterol 1998;1:1–7.
39. Ueki A, Otsuka M. Life style risks of Parkinson's disease: association between decreased water intake and constipation. J Neurol 2004;251(Suppl 7):18–23.
40. Kaye J, Gage H, Kimber A, Storey L, Trend P. Excess burden of constipation in Parkinson's disease: a pilot study. Mov Disord 2006;21:1270–1273.
41. Ashraf W, Pfeiffer RF, Park F, Lof J, Quigley EM. Constipation in Parkinson's disease: objective assessment and response to psyllium. Mov Disord 1997;12:946–951.
42. Siddiqui MF, Rast S, Lynn MJ, Auchus AP, Pfeiffer RF. Autonomic dysfunction in Parkinson's disease: a comprehensive symptom survey. Parkinsonism Relat Disord 2002;8:277–284.
43. Jost WH, Eckardt VF. Constipation in idiopathic Parkinson's disease. Scand J Gastroenterol 2003;38:681–686.
44. Edwards LL, Quigley EM, Harned RK, Hofman R, Pfeiffer RF. Characterization of swallowing and defecation in Parkinson's disease. Am J Gastroenterol 1994;89:15–25.
45. Verbaan D, Marinus J, Visser M, van Rooden SM, Stiggelbout AM, van Hilten JJ. Patient-reported autonomic symptoms in Parkinson disease. Neurology 2007;69:333–341.
46. 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;23:101–106.
47. Abbott RD, Ross GW, Petrovitch H, et al. Bowel movement frequency in late-life and incidental Lewy bodies. Mov Disord 2007;22:1581–1586.
48. Braak H, de Vos RA, Bohl J, Del Tredici K. Gastric alpha-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. Neurosci Lett 2006;396:67–72.
49. Bronner G, Royter V, Korczyn AD, Giladi N. Sexual dysfunction in Parkinson's disease. J Sex Marital Ther 2004;30:95–105.
50. O'Sullivan SS, Holton JL, Massey LA, et al. Parkinson's disease with Onuf's nucleus involvement mimicking multiple system atrophy. J Neurol Neurosurg Psychiatry 2008;79:232–234.
51. Bloch A, Probst A, Bissig H, Adams H, Tolnay M. Alpha-synuclein pathology of the spinal and peripheral autonomic nervous system in neurologically unimpaired elderly subjects. Neuropathol Appl Neurobiol 2006;32:284–295.
52. Minguez-Castellanos A, Chamorro CE, Escamilla-Sevilla F, et al. Do alpha-synuclein aggregates in autonomic plexuses predate Lewy body disorders? a cohort study. Neurology 2007;68:2012–2018.
53. Goldstein DS. Orthostatic hypotension as an early finding in Parkinson's disease. Clin Auton Res 2006;16:46–54.
54. Orimo S, Uchihara T, Nakamura A, et al. Axonal alpha-synuclein aggregates herald centripetal degeneration of cardiac sympathetic nerve in Parkinson's disease. Brain 2008;131:642–650.
55. Takatsu H, Nishida H, Matsuo H, et al. Cardiac sympathetic denervation from the early stage of Parkinson's disease: clinical and experimental studies with radiolabeled MIBG. J Nucl Med 2000;41:71–77.
56. Fujishiro H, Frigerio R, Burnett M, et al. Cardiac sympathetic denervation correlates with clinical and pathologic stages of Parkinson's disease. Mov Disord 2008;23:1085–1092.
57. Papapetropoulos S, Argyriou AA, Chroni E. No correlation between the clinical severity of autonomic symptoms (SCOPA-AUT) and electrophysiological test abnormalities in advanced Parkinson's disease. Mov Disord 2006;21:430–431.
58. Matsui H, Nishinaka K, Oda M, Komatsu K, Kubori T, Udaka F. Does cardiac metaiodobenzylguanidine (MIBG) uptake in Parkinson's disease correlate with major auto-

nomic symptoms? Parkinsonism Relat Disord 2006;12:284–288.
59. Reijnders JS, Ehrt U, Weber WE, Aarsland D, Leentjens AF. A systematic review of prevalence studies of depression in Parkinson's disease. Mov Disord 2008;23:183–189.
60. Leentjens AF. Depression in Parkinson's disease: conceptual issues and clinical challenges. J Geriatr Psychiatry Neurol 2004;17:120–126.
61. Robins AH. Depression in patients with Parkinsonism. Br J Psychiatry 1976;128:141–145.
62. Lieberman A. Depression in Parkinson's disease—a review. Acta Neurol Scand 2006;113:1–8.
63. Ravina B, Camicioli R, Como PG, et al. The impact of depressive symptoms in early Parkinson disease. Neurology 2007;69:342–347.
64. Santamaria J, Tolosa E, Valles A. Parkinson's disease with depression: a possible subgroup of idiopathic parkinsonism. Neurology 1986;36:1130–1133.
65. Shiba M, Bower JH, Maraganore DM, et al. Anxiety disorders and depressive disorders preceding Parkinson's disease: a case-control study. Mov Disord 2000;15:669–677.
66. Nilsson FM, Kessing LV, Bolwig TG. Increased risk of developing Parkinson's disease for patients with major affective disorder: a register study. Acta Psychiatr Scand 2001;104:380–386.
67. Nilsson FM, Kessing LV, Sorensen TM. Major depressive disorder in Parkinson's disease: a register-based study. Acta Psychiatr Scand 2002;106:202–211.
68. Schurmann AG, van den Akker H, Ensinck KTJL, et al. Increased risk of Parkinson's disease after depression: a retrospective cohort study. Neurology 2002;58:1501–1504.
69. Leentjens AFG, Van den Akker M, Metsemakers JFM, et al. Higher incidence of depression preceding the onset of Parkinson's disease: a register study. Mov Disord 2003;18:414–418.
70. Lauterbach EC, Freeman A, Vogel RL. Differential DSM-III psychiatric disorder prevalence and profiles in dystonia and Parkinson's disease. J Neuropsychiatry Clin Neurosci 2004;16:29–36.
71. Ishihara L, Brayne C. A systematic review of depression and mental illness preceding Parkinson's disease. Acta Neurol Scand 2006;113:211–220.
72. Walter U, Hoeppner J, Prudente-Morrissey L, Horowski S, Herpertz SC, Benecke R. Parkinson's disease-like midbrain sonography abnormalities are frequent in depressive disorders. Brain 2007;130:1799–1807.
73. Factor SA, McAlarney T, Sanchez-Ramos JR, Weiner WJ. Sleep disorders and sleep effect in Parkinson's disease. Mov Disord 1990;5:280–285.
74. van Hilten JJ, Weggeman EA, van der Velde GA, Kerkhof JG, van Dijk JG, Roos RAC. Sleep, excessive daytime sleepiness and fatigue in Parkinson's disease. J Neural Transm 1993;5:235–244.
75. Tandberg E, Larsen JP, Karlsen KA. A community-based study of sleep disorders in patients with Parkinson's disease. Mov Disord 1998;13:895–899.
76. Kumar S, Bhatia M, Behari M. Sleep disorders in Parkinson's disease. Mov Disord 2002;17:775–781.
77. Fabrinni 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;17:1026–1030.
78. Carter J, Carroll VS, Lannon MC, Vetere-Overfield B, Barker R. Sleep disruption in untreated Parkinson's disease. Neurology 1990;40(suppl 1):220.
79. Ferini-Strambi L, Franceschi M, Pinto P, Zucconi M, Smirne S. Respiration and heart rate variability during sleep in untreated Parkinson patients. Gerontology 1992;38:92–98.
80. Boeve BF, Silber MH, Ferman TJ, Lucas JA, Parisi JE. Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleopathy. Mov Disord 2001;16:622–630.
81. Schenck C, Mahowald MW. REM sleep behaviour disorder: clinical, developmental and neuroscience perspectives 16 years after its formal identification in SLEEP. Sleep 2002;55:281–288.
82. Zarranz JJ, Fernández-Bedoya A, Lambarri I, et al. Abnormal sleep architecture is an early feature in the E46K familial synucleinopathy. Mov Disord 2005;20:1310–1315.
83. Abbot RD, Ross GW, White LR, et al. Excessive daytime sleepiness and subsequent development of Parkinson disease. Neurology 2005;65:1442–1446.
84. Gagnon JF, Bedard MA, Fantini MD, et al. REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. Neurology 2002;59:585–589.
85. Iranzo A, Santamaria J, Rye DB, et al. Characteristics of idiopathic REM sleep behaviour disorder and that associated with MSA and PD. Neurology 2005;65:247–252.
86. Kumru H, Santamaria J, Tolosa E, Iranzo A. Relation between subtype of Parkinson's disease and REM sleep behaviour disorder. Sleep Med 2007;8:779–783.
87. Vendette M, Gagnon JF, Décary A, et al. REM sleep behavior disorder predicts cognitive impairment in Parkinson disease without dementia. Neurology 2007;69:1843–1819.
88. Frucht S, Rogers MD, Greene PE, Gordon PE, Fahn S. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 1999;58:1908–1910.
89. Gjerstad MD, Aarsland D, Larsen JP. Development of daytime somnolence over time in Parkinson's disease. Neurology 2002;58:1544–1546.
90. Kalaitzakis ME, Graeber MB, Gentleman SM, Pearce RK. The dorsal motor nucleus of the vagus is not an obligatory trigger site of Parkinson's disease: a critical analysis of alpha-synuclein staging. Neuropathol Appl Neurobiol 2008;34:284–295.