Premotor Parkinson's disease: Overview of clinical symptoms and current diagnostic methods

Michaela Kaiserova[a], Zuzana Grambalova[a], Sandra Kurcova[a], Pavel Otruba[a], Hana Prikrylova Vranova[b], Katerina Mensikova[a], Petr Kanovsky[a]

Parkinson's disease (PD) is characterized by typical motor symptoms. However, recent studies show several non-motor features that may precede the development of the motor symptoms of PD. The best known premotor symptoms include hyposmia, REM sleep behavior disorder (RBD), constipation, and depression; other symptoms are excessive daytime somnolence, orthostatic hypotension and symptomatic hypotension, erectile or urinary dysfunction, musculoskeletal symptoms, pain, and global cognitive deficit. In this review, we summarize currently available diagnostic methods for these symptoms. We also briefly summarize neuroimaging, polyneuropathy, peripheral markers, and cerebrospinal fluid biomarkers that may be used in the early diagnosis of PD.

Key words: Parkinson's disease, premotor symptoms, diagnostic methods

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[a]Department of Neurology, Faculty of Medicine and Dentistry, Palacky University and University Hospital, Olomouc, Czech Republic
[b]Neurology Outpatient Clinic "St. Moritz", Olomouc, Czech Republic
Corresponding author: Michaela Kaiserova, e-mail: michaela.kaiserova@fnol.cz

INTRODUCTION

Parkinson's disease (PD) is characterized by typical motor symptoms caused by degeneration of the substantia nigra. However, recent studies show that Lewy pathology in PD is not only present in the midbrain; it is a diffuse synucleinopathy affecting both the central and peripheral nervous system, spreading in a caudo-rostral pattern[1,2]. This widespread pathology results in a number of non-motor symptoms, some of which may be present for years before the development of the typical motor symptoms of PD.

The Movement Disorders Society proposed research diagnostic criteria for prodromal PD in 2015 (ref.[3]) and updated them in 2019 (ref.[4]). These criteria comprise symptoms with a predictive value for developing PD that has been documented in prospective studies. The criteria have been validated on the general population[5], REM sleep behavior disorder patients[6], and LRRK2 mutation carriers[7]; the criteria seem to be a promising tool in identifying PD in the premotor stage[5,8,9].

The best known premotor symptoms of PD include hyposmia, REM sleep behavior disorder (RBD), constipation, and depression; other non-motor features are excessive daytime somnolence, orthostatic hypotension and symptomatic hypotension, erectile or urinary dysfunction, and global cognitive deficit. Pain, sometimes accompanied by musculoskeletal symptoms, may also occur in the premotor phase of PD.

The aim of this review is to summarize the currently available methods for diagnosing the premotor symptoms of PD which may help in the early diagnosis of PD.

Olfactory functions

Olfactory impairment is common in PD; its prevalence is estimated to be 50-90% (ref.[10]). Olfactory impairment often precedes motor symptoms by years; idiopathic olfactory loss is considered a risk factor for PD (ref.[11-13]).

Questionnaires may be used as a screening instrument for olfactory dysfunction. Questions concerning olfactory functions are usually part of more complex questionnaires, such as the Non-Motor Symptoms Questionnaire (NMSQest) (ref.[14]), the International Parkinson and Movement Disorder Society – Non-Motor Rating Scale (MDS-NMS) (ref.[15]), and the Non-Motor Symptoms Scale for Parkinson's Disease (NMSS) (ref.[16]).

Many PD patients are unaware of their impairment and overestimate their ability to smell, which makes self-report questionnaires unreliable[17,18]. For this reason, a gold standard in daily practice are psychophysical tests[19]. These tests are based on the presentation of different odors to the subject. The test that was first developed and is still widely used due to its easy administration is the University of Pennsylvania Smell Identification Test (UPSIT). This test, developed in the United States, provides 40 odors; the subject is supposed to identify the odor by choosing the best result from the offered selection[20]. Cultural and social factors may be a limitation of this test, as some odors are not familiar in some countries. This possibility has led to several local adaptations of the test[21-25]. One shorter version of UPSIT is the National Health and Nutrition Examination Survey (NHANES) eight-item odor identification test (Pocket Smell Test™) (ref.[26]). There is a twelve-item test, called the Brief Smell Identification Test (B-SIT) and also known as the Cross-Cultural Smell Identification Test (CC-SIT) (ref.[27]).

Another test, more popular in Europe, is the Sniffin' Sticks test. This test is able to test all three olfactory qualities: odor-identification, odor-discrimination, and olfactory threshold[28]. To find the olfactory threshold, 16 trios of sticks are used. In each trio, one stick is impregnated with n-butanol or 2-phenylethanol diluted in a solvent in a different concentration. The subject is supposed to identify this stick from among the other sticks containing only the solvent. For the odor-discrimination testing, 16 trios of sticks are also used. In each trio, two sticks are impregnated with the same odor and the third one is impregnated with a different odor. The subject is then required to identify the stick with the different odor. The last part of the test is focused on odor identification. Sixteen odors are given and the subject must choose one from four suggestions[28,29]. The disadvantage of this validated test is that it is time consuming. However, some studies show that the odor-identification subtest may be equal to the whole test battery[30-32].

The Snap and Sniff® Threshold test (S&S-T) was recently developed for detecting olfactory thresholds. This test uses 20 smell wands; five contain no odorant, the others contain diluted 2-phenylethanol in increasing concentrations[33].

There are other smell tests, such as SMELL-S and SMELL-R that test olfactory sensitivity and olfactory resolution[34], fast Q-Sticks test presenting three odors in felt-tip pens[35], the Connecticut Chemosensory Clinical Research Center (CCCRC) identification test measuring odor-identification and threshold[36], the Smell Diskettes Test using eight different odors with a high degree of familiarity in Central Europe[37], the Barcelona Smell Test-24 (BAST-24) with 24 odors[38], a 4 min odor identification test with 12 odors in sticks[39], the European Test of Olfactory Capabilities (ETOC) testing odor-identification and threshold, validated in three European countries[40], the three-item Q-SIT (ref.[41]), the Odor Stick Identification Test using 13 odors in microcapsules incorporated into a stable cream and encased like a lipstick[42], and the 16-item Scandinavian Odor Identification Test[43].

Psychophysical tests are non-invasive and easily available, and many are inexpensive and not time consuming, so they may be used to diagnose olfactory dysfunction in PD, even in the premotor phase. The limitation is that despite the high sensitivity for predicting PD, the specificity is low, because up to one in three elderly people have olfactory loss of various other etiologies[44]. Therefore, smell tests alone are not sufficient to diagnose PD in the premotor phase. Additional tests of other premotor symptoms must be conducted.

An objective method to test olfactory function is electrophysiologic recording. In PD patients, olfactory event-evoked potentials (OERP) returned abnormal results[45,46]. Electrophysiologic recordings are rarely used in clinical practice because of the complexity to perform them and economic aspects[47].

The sniff magnitude test may be an alternative to psychophysical tests in PD. This test is based on the reflex-like response to malodors by quantifying the decrease of inhalation when a malodorous stimulus is encountered[48,49]. This test seem to be less sensitive than other measures[50,51], and does not give information on clinically relevant olfactory functions such as odor identification, differentiation, and threshold[52]. It may nevertheless be a good alternative for investigating PD patients with dementia.

As mentioned above, current olfactory tests have low specificity for diagnosing premotor PD. To become more specific, recent PD studies have focused on other methods, such as biopsy of olfactory epithelium, measuring the olfactory bulb volume, and functional neuroimaging.

Olfactory bulb and olfactory mucosa biopsies are based on the recent finding that α-synuclein can be detected in peripheral tissues such as the gastrointestinal tract, salivary glands, skin, retina, heart, adrenal gland, and olfactory tissue[53,54]. Positive α-synuclein staining of olfactory bulb specimens ranged from 8% to 100% for PD compared to 2-100% in a control group[53,54]. This examination is invasive and not without risk and all studies published thus far were restricted to postmortem investigations. In vivo tests have been restricted to the olfactory mucosa. Witt et al. found no specific changes in the nasal mucosa of PD compared to patients who were hyposmic for other reasons; moreover, α-synuclein was also observed in normosmic controls[55].

Olfactory bulb volume is possible to measure using a 1.5 Tesla MRI (ref.[56]). Several studies showed a correlation between olfactory bulb volume and olfactory function[57-59]. In PD, however, the results are not convincing. Some studies showed reduced olfactory bulb volume on both sides[60-62]; other studies did not find any difference between PD patients and healthy controls[63,64]. Hakyemez et al. even found increased olfactory bulb volume in Hoehn &Yahr stage 1 and 2 (ref.[65]). These different results indicate that additional studies will be needed to see whether the measurement of olfactory bulb volume may become a useful and reliable method for diagnosis of premotor PD.

Autonomic dysfunction

Autonomic dysfunction is present in early PD; some symptoms may precede the motor symptoms of the disease by many years[66-68].

The most reliable autonomic premotor symptom is constipation; other symptoms are erectile and urinary dysfunction and orthostatic hypotension or symptomatic hypotension[69-75].

Constipation

The Movement Disorder Society (MDS) Task Force on Rating Scales for PD evaluated scales for gastrointestinal-related autonomic symptoms in PD that were used previously as outcome measures in studies with PD patients[76]. Scales were rated as recommended if they were valid, reliable, and sensitive and had been used in clinical studies beyond the group that developed it. There was no recommended scale for constipation. The Rome III Criteria may be used to define constipation; however, this scale has not been validated for the PD population.

Global scales addressing dysautonomia and nonmotor symptoms, including constipation, are used more often.

The Scales for Outcomes in PD-Autonomic (SCOPA-AUT) (ref.[77]) and the Nonmotor Symptoms Questionnaire for PD (NMSQuest) (ref.[14]) were recommended. The Nonmotor Symptoms Scale (NMSS) (ref.[16]) was also suggested.

Apart from questionnaires, laboratory tests may also detect gastrointestinal dysfunction. PD patients have prolonged colonic transit time (CCT) (ref.[78,79]); abnormal results may be present also in patients with no subjective constipation symptoms[80,81]. The most commonly used technique is measuring CCT using radio-opaque markers. A defined number of these markers is ingested, an abdominal x-ray is performed 24 h after the ingestion of the last capsule, and the estimated transit time is measured from the number of retained markers[82,83]. This simple method may have some potential in diagnosing prodromal PD; however, there are still no studies using this method in premotor PD.

Constipation in PD is probably caused not only by delayed CCT, but also by anorectal dysfunction, which can be measured by anorectal manometry or by defecography[81,84]. Published studies are mostly based on small patient samples and variable methodology[84] so the possible use of these methods in diagnosing prodromal PD have to be established on future larger studies.

Erectile dysfunction

PD is associated with increased risk of sexual dysfunction and this dysfunction may be present in the preclinical stage of PD (ref.[85]). Problems with sexual dysfunction are reported especially by men[85,86]. Studies dealing with sexual dysfunction in women have produced controversial results[86,87]. Erectile dysfunction has been found to be a risk factor of PD (ref.[71,75]) but the prevalence of erectile dysfunction in the non-parkinsonian population is also significant[88,89] so this symptom must be evaluated carefully in context with other premotor symptoms. Questionnaires are currently preferred in diagnosing erectile dysfunction. One widely used questionnaire is the International Index of Erectile Function (IIEF) (ref.[90-92]). Another questionnaire concerning sexual dysfunction that has been used in PD studies is the Arizona Sexual Experience Scale (ASEX), an easily applicable five-item questionnaire[93,94]. The Female Sexual Function Index (FSFI) is focused on women[95]. Questions concerning sexual function are also a part of global scales addressing dysautonomia in PD – SCOPA-AUT (ref.[77]), NMSQuest (ref.[14]), and NMSS (ref.[16]).

Urinary dysfunction

Up to 71% of PD patients report lower urinary tract symptoms. Patients most commonly complain about storage symptoms, such as nocturia, urgency, and daytime frequency; up to 26% of men and 28% of women with PD experience urinary incontinence[96]. Voiding symptoms are less common, but may also occur in PD; patients have higher rates of difficulty initiating urination, poor stream, straining[97]. Questionnaires are a useful instrument for detecting urinary dysfunction in PD. There are global dysautonomia scales comprising urinary symptoms; these scales are mentioned above. Scales focused on urinary dysfunction that were used in the PD population are the American Urological Association Symptom Index (AUA-SI) (ref.[98]) and the International Prostate Symptom Score (I-PSS) (ref.[99]) for men and the short form of the Urogenital Distress Inventory (UDI-6) (ref.[100]) for women. Another questionnaire used in PD is the Overactive Bladder Questionnaire (OAB-q) (ref.[101,102]). This questionnaire has 36 items but there is also a short eight-item form.

Urodynamic studies use objective methods that assess the lower urinary tract function. In one study, urodynamic tests revealed abnormal findings in 82% of early and untreated PD patients; this was more than the questionnaire-based subjective symptoms of urinary dysfunction (64%) (ref.[103]). These findings suggest that urinary dysfunction in the early stages of PD may be asymptomatic or have little influence on quality of life, so the symptoms may be overlooked[103].

Orthostatic hypotension and symptomatic hypotension

Orthostatic hypotension (OH) is defined as a sustained reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mm Hg within 3 min of standing or a head-up tilt to at least 60° on a tilt table[104]. It has been shown that OH may precede the motor symptoms of PD (ref.[68,75,105,106]). OH may be symptomatic or asymptomatic and the symptoms may vary across patients from lightheadedness, to dizziness, to pre-syncope and syncope. Some patients report weakness, fatigue, cognitive slowing, leg buckling, visual blurring, neck pain, headache, and orthostatic dyspnea of chest pain[104].

The MDS analyzed the scales and questionnaires for OH that were used in PD (ref.[107]). Most of them were larger scales or questionnaires globally assessing nonmotor and autonomic functions. Some scales detect OH-related symptoms and provide information on the severity and/or frequency. From these scales, the ones recommended with limitations were SCOPA – AUT (ref.[77]) and the Composite Autonomic Symptom Scale (COMPASS) with the orthostatic subsection[108]. The Non-Motor Symptoms Scale for Parkinson's Disease (NMSS) (ref.[16]) was categorized as suggested because its use has not been reported outside the validation study that later changed[109,110]. The Orthostatic Grading Scale (OGS), a five-item questionnaire focused only on OH (ref.[111]) was also suggested because it needed to be validated on a PD population. Later the scale was validated on a group in Korea[112].

There are scales that may be used as screening tools for OH but do not score the severity/frequency of orthostatic symptoms. The strongest clinimetric testing has been performed on the NMS Quest (ref.[14]).

An easily performed objective test for OH is a measurement of blood pressure after at least 5 min in a supine position and then after 1 and 3 min of standing[113]. The passive head-up tilt test (HUT) is recommended if the active standing test is negative and the patient history is suggestive of OH, and in patients with severe motor impairment where it is not possible to perform an active orthostatic test[114]. In cases where the supine-to-standing

test of HUT is difficult to perform, a seated-to-standing orthostatic test may be an alternative[115,116].

REM sleep behavior disorder (RBD) and excessive daytime somnolence

RBD is considered to be one of the strongest clinical markers of prodromal neurodegenerative synucleinopathy[6,117-119]. A definite diagnosis of RBD is determined according to the International Classification of Sleep Disorders-3 (ICSD-3) (ref.[120]), where polysomnography (PSG) plays an essential role. PSG remains the gold standard for diagnosis of RBD. However, questionnaires are still useful in clinical practice. Several screening questionnaires were developed for screening of RBD. A commonly used questionnaire is the 10-item RBD screening questionnaire (RBDSQ), validated on PD populations[121-125]. Another questionnaire focused solely on RBD is the Sleep Behavior Disorder Single Question Screen (RBD1Q) (ref.[126]).

Based on two studies, excessive daytime somnolence is considered a premotor feature of PD (ref.[127,128]). To assess daytime sleepiness, the Epworth sleepiness scale (ESS) was developed[129] and has been used in PD populations[130-132].

There are questionnaires used in PD that cover both nocturnal sleep disorders (including RBD) and excessive daytime sleepiness[133]. The Parkinson's Disease Sleep Scale (PDSS) (ref.[134]), the revised version PDSS-2 (ref.[135]), and the Scales for Outcomes in PD-Sleep (SCOPA-Sleep) (ref.[136]) were designed and validated for PD populations. Questions on sleep disturbances including excessive daytime somnolence are included in general nonmotor questionnaires – NMSQuest (ref.[14]), NMSS (ref.[16]), and MDS-UPDRS Part I (ref.[137]).

Depression

Several studies have shown that depression increases the risk of PD (ref.[75,138-141]), but its sensitivity and specificity is low[44]. Depression rating scales used in PD studies were analyzed with estimations of the sensitivity and specificity of each test in PD populations[142,143]. Scales suitable for screening purposes are the 30-item and 15-item Geriatric Depression Scale (GDS-30, GDS-15) (ref.[144,145]), the Beck Depression Inventory (BDI) (ref.[146]), The Montgomery Åsberg Depression Rating Scale (MADRS) (ref.[147]), the Hamilton Rating Scale for Depression (HAMD-17) (ref.[148]), and the Hospital Anxiety and Depression Scale (HADS) (ref.[149]). A crude screening instrument for depression is also the MDS-UPDRS Part I (ref.[137]). To measure the severity of depression, HAMD-17, MADRS, BDI, or the Zung Self-Rating Depression Scale (SDS) (ref.[150]) may be used.

Cognitive deficit

Cognitive deficit was recently added to the prodromal symptom spectrum of PD (ref.[4]) on the basis of the results of three studies[151-153]. The most frequent cognitive deficit is executive dysfunction, the second most frequent is memory; there can also be deficits in attention and visuospatial functions; and global cognitive impairment has also been described[154]. Detailed neuropsychological testing is a gold standard to assess the most commonly affected cognitive domains. This testing, however, is time consuming and not available in all settings. Therefore, global cognitive tests covering the most relevant cognitive domains were evaluated[155]. Three scales were recommended without caveats: the Mattis Dementia Rating Scale Second Edition (DRS-2) (ref.[156]), which takes about 20 -30 min to administer and is divided into 5 subscales: Attention, Initiation/Perseveration, Construction, Conceptualization, and Memory. Another recommended scale was the Montreal Cognitive Assessment (MoCA) (ref.[157]), taking about 10 min to administer and assessing memory, visuospatial skills, attention and concentration, executive functions, language, conceptual thinking, calculations, and orientation. The last recommended test was the Parkinson's Disease-Cognitive Rating Scale (PD-CRS) (ref.[158]), taking about 20 min to administer and covering both cortical functions, such as naming and copy drawing of a clock, and subcortical functions, including attention, working memory, verbal memory, visuoconstruction, alternating, and action fluency. The widely used 30-point Mini-Mental State Examination (MMSE) (ref.[159]) was rated only as suggested for PD patients, as other cognitive scales have shown better capacity and sensitivity for detecting dementia in PD, and because MMSE does not adequately assess executive and visuospatial functions, which are characteristically affected in PD and is also not sensitive to detecting early stages of cognitive deterioration.

Pain

Pain occurs early in the disease course, even as a premotor symptom of PD (ref.[160-163]). The MDS evaluated available ratings scales for pain that may be used in PD (ref.[164]). The only recommended scale for pain intensity rating was the King's PD Pain Scale[165]. This scale encompasses seven pain domains seen in PD: musculoskeletal, chronic, fluctuation-related, nocturnal, orofacial, discoloration/swelling, and radicular pain. When assessing scales in terms of pain syndromic classification, the MDS evaluated the King's PD Pain Scale as only suggested because it has not been adequately validated. The Douleur Neuropathique 4 (DN4) was recommended with caution due to lack of clinimetric data in PD (ref.[166]).

Small fiber neuropathy

Both large and small fiber neuropathy may be associated with PD (ref.[167-169]). There are reports that PD may be associated also with motor neuron disease[170,171]. A recent study suggested that small fiber pathology may precede the development of motor symptoms of PD (ref.[172]). Small fiber functions may be investigated bedside by responsiveness to heat, cold, and pain evoked by pinprick. There are also several specific neurophysiological and pathological techniques for detecting small fiber pathology, such as skin biopsy, quantitative sensory testing, quantitative sudomotor axon reflex test, corneal confocal microscopy, microneurography, and electrical and laser evoked potentials[173].

Neuroimaging

Except for clinical features, several neuroimaging methods can help with the diagnosis of premotor PD. The wide range of imaging modalities can be divided into three groups[174]: targeting dopaminergic function in the basal ganglia using radio-labelled ligands, detected by single photon emission computed tomography (SPECT) or positron emission tomography (PET) (ref.[175,176]); direct imaging of the substantia nigra by transcranial sonography detecting increased echogenicity of substantia nigra[177,178] or brain MRI focusing on brainstem structures[179-181]; and imaging brain network activity with measuring metabolic activity, changes in blood oxygenation of regional cerebral blood flow[174,182,183].

Peripheral markers

^{123}I-metaiodobenzylguanidine (MIBG) uptake is decreased in PD, indicating myocardial postganglionic sympathetic denervation[184] and seems to be promising in the diagnosis of premotor PD (ref.[185,186]).

Detection of phosphorylated α-synuclein in skin biopsies seems to be a sensitive and specific marker of PD and also of premotor PD (ref.[4,187,188]). Submandibular glands[187,189] and gastrointestinal tract mucosa are also tested for α-synuclein in premotor PD (ref.[187]). In one study, α-synuclein was found in the enteric mucosa in the same manner in the PD patients and the controls[190].

Cerebrospinal fluid

Studies usually focus on biomarker candidates for distinguishing between PD and controls or on differentiating PD from other neurodegenerative disorders. The biomarkers may be divided into six categories[191,192]. A: Neurotransmitters and neuromodulators; Goldstein et al. found low CSF DOPA and/or low CSF 3,4-dihydroxyphenylacetic acid (DOPAC), the main neuronal metabolite of dopamine, in people with multiple risk factors for PD who subsequently developed clinical features of PD (ref.[193]). B: Oxidative stress markers; mutations in DJ-1 gene/PARK7 are associated with PD; however, the results of the studies measuring CSF DJ-1 levels are not yet conclusive[191]. C: Inflammatory and immunological markers; several cytokines were found to be increased in PD, such as β2-microglobulin and IL-8 (ref.[194]), IL-6 and IL-1-B were increased in cognitively impaired PD (ref.[195]). D: Growth factors; in one study, brain-derived neurotrophic factor (BDNF) was found to be increased in PD patients[194]. E: Proteins involved in PD pathology; a commonly studied biomarker is α- synuclein. This protein has a tendency to be lower in PD; however, not all published studies have consistent results[196-198]. Studies with CSF total tau, phosphorylated tau, and amyloid-β protein and its variants also had inconclusive results[191,194,199-201]. Neurofilament light chain (NfL) seems to be useful in differential diagnosis of PD and atypical parkinsonism[200,202]. Clustering was found to be increased in PD (ref.[199,203-205]). One study found decreased YKL-40 in PD patients compared to controls[206]. F: Other. Although many studies try to establish potential CSF biomarkers of PD, the application of CSF examination in the diagnosis of premotor PD is still limited. Only a few studies have focused on the premotor stages of PD; sampling techniques and analysis procedures differ across the studies, and the results are often conflicting. Larger longitudinal studies will be necessary to establish CSF biomarkers of premotor PD.

In conclusion, recent studies show that there are several non-motor symptoms with predictive value for the development of PD. They are currently being tested in research settings due to the lack of effective neuroprotective therapy. However, as soon as an adequate treatment is available, it will be a priority for clinicians to establish the diagnosis of PD in the early/premotor stages in order to preserve the patients' quality of life.

Search strategy and selection criteria

We searched PubMed, Web of science and Google scholar using the keywords Parkinson's disease, premotor symptoms, olfactory functions, autonomic dysfunction, constipation, erectile dysfunction, urinary dysfunction, orthostatic hypotension, REM sleep behavior disorder, depression, cognitive functions, pain, small fibre neuropathy, neuroimaging, cerebrospinal fluid.

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