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REVIEW ARTICLE

Who Can Diagnose Parkinson's Disease First? Role of Pre-motor Symptoms

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In 1817, James Parkinson described the disease which bears his name. The disease was defined as a neurological syndrome characterized by tremor, rigidity, and slowness of movements. Almost one hundred years later, degeneration of neurons in the substantia nigra and low levels of dopamine were identified as the putative cause of the disease, thus the disease remained as a pure neurological disorder. In the late 1990s, non-motor symptoms of the disease began to gain interest because of their clinical relevance, as well as for their potential role in broadening the understanding of the pathophysiological mechanisms involved. In the last decade, focus has shifted to the pre-motor symptoms, those non-motor symptoms that present years before the motor onset of the disease. The main premotor symptoms include rapid eye movement sleep behavior disorder, hyposmia, constipation and depression. Subjects with these symptoms usually are not initially seen by a neurologist, and by the time they are consulted neuronal loss in the substantia nigra is over 50%. This review summarizes the overall relevance of non-motor symptoms, their frequency and their pathophysiological implications. Also, the importance of pre-motor symptoms, and the role of specialists other than neurologists in diagnosing subjects with Parkinson's disease is discussed. Two hundred years after the first description of the disease, it is now evident that Parkinson's disease is a systemic disease and a multispecialty team approach is mandatory.

Key Words: Parkinson's disease, Non-motor, Pre-motor, Diagnosis.

Introduction

Parkinson's disease (PD) has been traditionally hallmarked by the presence of motor symptoms including the ''classic triad'' of tremor, rigidity, and bradykinesia. Nevertheless, in the last decade the presence and relevance of non-motor symptoms has been widely recognized. One of the major aspects of the non-motor symptoms is the fact that some of them can appear several years before the motor onset of the disease (1). Currently, PD is diagnosed by the presence of parkinsonism (i.e. bradykinesia plus some other motor feature); unfortunately, a 50% reduction in dopaminergic nigrostriatal cells is required for motor symptoms to be clinically apparent (2). Consequently, treatment is usually started late in the course of the neurodegenerative process, is exclusively symptomatic, and probably too late for any neuroprotective effect to be achieved. The identification of subjects with PD before the motor symptoms develop can only be achieved by the early recognition of non-motor symptoms; which in most cases could be done by physicians other than neurologists.

In this review, we present the current evidence regarding the role of premotor symptoms, their pathophysiological implications, and the relevance of a multidisciplinary approach to diagnose PD as early as possible.

Non-motor Symptoms in PD

PD non-motor symptoms (NMS) include more than 30 different symptoms comprising almost every system. These NMS can be broadly divided in the following categories: sensory features, neuropsychiatric and cognitive symptoms, sleep disorders, and autonomic dysfunction (3). Table 1 summarizes the main non-motor symptoms that can be present in patients with PD. Some of these NMS are non-dopaminergic, while

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Table 1. Main non-motor symptoms in subjects with Parkinson's disease

Category	Non-motor symptom
Sensory symptoms	Hyposmia, impaired color vision, blurred vision, diplopia, pain
Neuropsychiatric symptoms	Hallucinations, psychosis, anxiety, depression, apathy, impulse control disorders
Cognitive symptoms	Early cognitive dysfunction, dementia
Sleep disorders	Rapid-eye movement sleep behaviour disorder, restless leg syndrome, daytime sleepiness, sleeps attacks, periodic limb movements
Cardiovascular dysautonomia	Postural hypotension, blood pressure variability, nocturnal hypertension, edema
Gastrointestinal dysautonomia	Reduced gastric emptying, constipation, sialorrhea
Genitourinary dysautonimia	Urinary frequency, nocturia, detrusor hyper-reflexia, reduced libido, erectile dysfunction

others respond to dopaminergic treatment (4). Non-dopaminergic symptoms are the result of abnormalities in other neurotransmitters such as noradrenaline, serotonin (5-hydroxytryptamine; 5-HT), glutamate, γ-aminobutyric acid (GABA), acetylcholine and neuropeptides. Deficits in noradrenaline lead to some symptoms such as constipation, urinary disorders and orthostatic hypotension. Cognitive impairment is partially the result of the dopaminergic deficit but also a cholinergic and noradrenergic deficit. Sleep disorders and some neuropsychiatric symptoms are related to serotonin disorders. Nevertheless, it should be mentioned that most of the non-motor symptoms share disruptions in both dopaminergic and non-dopaminergic pathways (5).

Symptoms such as depression, restless leg syndrome, constipation and pain are considered responsive to dopaminergic therapy (6). Conversely, some symptoms such as impulse control disorders, edema and visual hallucinations are related to PD treatment (7). Moreover, some symptoms such as apathy and impulse control disorder have been considered as part of a continuous behavioural spectrum involving hypo- and hyperdopaminergia (8).

Another important feature of NMS is their fluctuating pattern. Similar to motor symptoms, NMS may fluctuate accordingly to the ''on'' (with medication effect) or ''off'' state (without medication effect). The main NMS reported to fluctuate include neuropsychiatric symptoms, such as depression and anxiety, and autonomic symptoms including hypotension, constipation, sexual disorders and bladder dysfunction (9).

Last, but not least, NMS have a partially-defined pattern related to the disease progression. Some NMS are usually seen late in the course of the disease (i.e. dementia, psychosis, orthostatic hypotension), while others are present in early stages (i.e. fatigue, pain, anxiety). But more relevant from the diagnostic and pathophysiological stand-point are those symptoms which develop years, or even decades, before the motor onset of the disease (10). These symptoms include hyposmia, rapid-eye movement (REM) behaviour disorder (RBD), constipation and depression (11–13). A recent meta-analysis proved that these symptoms are more prevalent in subjects with PD than in controls. Hyposmia is present in 75.5% in cases vs. 19.1% in controls, followed by constipation (50 vs. 17.7%), rapid eye movement sleep behavior disorder (37.0 vs. 7.0%), and depression (36.6 vs. 14.9%) (14).

Role of Non-motor Symptoms in the Pathophysiology of PD

From a histopathological view, PD is classified as a synucleinopathy; which is hallmarked by the presence of Lewy bodies (cellular inclusions of alpha–synuclein) in the brain. One of the recent milestones on PD pathophysiology is the model proposed by Braak et al. In this model, the neuropathological process during the development of premotor PD is characterized by the appearance of Lewy bodies with a progressive and predictable sequence in localizations other than the substantia nigra (15). This spread of α-synuclein is still the most helpful concept too understand the clinical variability and symptomatology seen in PD (16).

The Braak model, also known as Braak theory, Braak staging, or Braak's hypothesis, proposes a neuropathological staging scheme divided in six stages following a caudo-rostral progression. Stages 1 through 3 are considered as presymptomatic (or premotor) (17).

In stage 1, Lewy pathology appear in the olfactory bulb, anterior olfactory nucleus, and dorsal motor nucleus of the vagus nerve. Symptoms such as hyposmia and dysautonomia are expected to develop during this stage.

In stage two, α-synuclein inclusions appear in the medulla oblongata followed by lesions in the locus coeruleus in the pons. Lesions in the locus coeruleus, a noradrenergic nucleus of the ascending reticular activating system, can give rise to sleep-wake cycle and rapid eye movement sleep disturbances.

In stage three, Lewy body pathology progresses reaching the amygdala, the cholinergic nuclei of the basal forebrain, and finally, the pars compacta of the substantia nigra. The amygdala is part of the limbic system and is associated with emotional processes and learning, thus disruptions in this nucleus can lead to anxiety and depression.

Stages four through six are related to the presence of evident clinical motor manifestations of the disease. In Stage four, the cerebral cortex is also involved. In stage five, progression of

pathological changes extends to high-order sensory association and prefrontal areas; and in stage six the α-synuclein spreading has fully invaded the neocortex (18).

The evidence of a progressive process starting in the brainstem led researchers to look for α-synuclein inclusion bodies outside the central nervous system. Wakabayashi et al described the presence of Lewy bodies in the Auerbach's and Meissner's plexuses in the late eighties (19); but Braak et al were the first to link the neuronal damage from the enteric to the central nervous system (20). On the other hand, Iwanaga et al described the presence of Lewy bodies in the postganglionic sympathetic neurons of the heart (21); while Orimo et al correlated decreased cardiac uptake of meta-iodobenzylguanidine (MIBG) on PET scans with loss of cardiac sympathetic nerve in early PD (22).

The biochemical and anatomo-clinical correlation of these symptoms has been summarized in Table 2.

Non-motor symptoms as Premotor Biomarkers

REM Sleep Behavior Disorder

RBD is a sleep disorder characterized by the patient physically acting out vivid dreams (dream-enacting behaviour). The dreams are usually unpleasant and the acting out is frequently accompanied by vocal sounds and sudden, violent movements of their arms and legs. Interestingly, James Parkinson described this symptom 200 years ago; in his ''Essay on the Shaking Palsy'' he wrote ''In this stage the sleep becomes much disturbed. The tremulous motion of the limbs occurs during sleep, and augment until they awaken the patient, and frequently with much agitation and alarm'' (23). Definite diagnosis of RBD requires confirmation by full-night polysomnography (PSG).

It has been described that patients with idiopathic RBD (iRBD) are at a very high risk of developing a neurodegenerative disease, mainly a synucleinopathy such as PD. Postuma et al. followed-up 279 patients with iRBD finding a phenocoversion (change from one disease to another) rate of 25% at three years and 41% after five years (24). Iranzo et al reported that 45% of a sample of 44 patients diagnosed with iRBD developed a neurological disorder within a mean of 11.5 years from the reported onset of RBD (25). More recently, Iranzo et al reported that the risk of a neurodegenerative disease, including PD, from the time of iRBD diagnosis was almost 76% at ten years, and 91% at 14 years (26).

From a pathogenic point of view, as mentioned before disruptions of GABAergic neurons in the locus coeruleus can lead to RBD (27). Presence of a pathological process in this location before the appearance of degeneration in the substantia nigra supports the caudal-to-rostral directionality suggested by the Braak staging model. On the other hand, evidence from neuroimaging studies is controversial; Iranzo et al. studied 43 iRBD subjects who underwent a dopamine transporter (DAT) single-photon emission computed tomography (SPECT) and transcranial sonography (TCS) of the substania nigra. They concluded that findings in patients with iRBD were almost identical to those found in subjects with PD (28). Nevertheless, Kim et al reported that not all subjects with iRBD will exhibit a dopaminergic defict on DAT SPECT (29). Overall, it has been reported that 20−40% of iRBD patients have abnormal DAT imaging (30).

Regarding histopathology, a study with 172 subjects with RBD with or without a known neurological disorder showed that 94% had pathology consistent with a synucleinopathy (31). Also, patients with PD and RBD (not confirmed by PSG) appear to have greater density and range of synuclein pathology in comparison to those with PD alone (32).

Hyposmia

Hyposmia is defined as partial loss of the ability to perceive or detect smells. In clinical practice, hyposmia is diagnosed as an abnormal performance on a smell identification test. Similar to iRBD, hyposmia has been well identified as a strong risk marker for developing a neurodegenerative disease (33).

In the case of PD, Ponsen et al reported that hyposmia in first-degree relatives of PD patients is related with a risk of developing PD of 12.5% over a five year period (34).

According to the Braak propagation model, deposition of alpha-synuclein in the olfactory bulb is seen at stage one. A recent study demonstrated the presence of alpha-

Table 2. Correlates of some non-motor symptoms with the brain region affected, impaired neurotransmitter, clinical stage and pathological stage

Non-motor symptom	Brain region	Main neurotransmitter	Clinical stage	Braak stage
Hyposmia	Olfactory bulb	Acetylcholine	Prodromal	Stage 1
Constipation	Enteric nervous system	Acetylcholine	Prodromal	Stage 1
Sleep disturbance	Hypothalamus and reticular formation	Dopamine and serotonin	Prodromal	Stage 2
Depression	Limbic and cortical areas	Dopamine and Noradrenaline	Prodromal	Stage 3
Pain	Basal ganglia, locus coeruleus, raphe nucleus, amygdala and thalamus	Dopamine, serotonin and noradrenaline	Clinical PD	Stage 4
Hallucinations	Occipital Cortex	Dopamine	Clinical PD	Stage 5
Early cognitive dysfunction	Frontal cortex	Dopamine	Clinical PD	Stage 5
Dementia	Temporal, parietal, occipital lobes.	Acetylcholine	Clinical PD	Stage 6

PD, Parkinson's disease.

synuclein in the olfactory epithelium in six of the eight PD patients included (35). In addition, α-synuclein deposit has been identified along neurons throughout the olfactory pathway (36).

Studies with functional magnetic resonance imaging have also demonstrated that activity in brain areas related to olfaction (amygdala and hippocampus) are reduced (37). As with iRBD, hyposmia is associated with an abnormal DAT SPECT (38), as well as with an abnormal substania nigra TCS (39).

Constipation

Gastrointestinal motility is impaired in PD, resulting is symptoms like dysphagia, abnormal gastric emptying and constipation. From these symptoms, only constipation may precede the onset of motor symptoms (40). The prevalence of constipation based on Rome III criteria has been reported to be of 27% (41) but most studies report a median of 40–50% depending on the definition and clinical tool used (42).

As mentioned before, PD may begin in the olfactory bulb or in the enteric nervous system (43). Lewy bodies have been found in the myenteric and submucosal plexuses throughout the enteric nervous system (19) with higher involvement in the lower esophagus in comparison to colon. Consequently, a rostrocaudal gradient of α-synuclein in the enteric nervous system has been proposed although this theory is still controversial (44).

Moreover, Lewy bodies in the enteric system supports the ''dual hit'' theory for development and progression of PD. This theory proposes two ways of entrance of a probable pathogen, for example a virus or a prion-like protein, to the brain. The unknown pathogen gains entrance through the enteric nervous system, affecting the fibers of the vagus nerve, and continuing its progression in a retrograde transport to the vagal dorsal motor nucleus in the medulla oblongata. Simultaneously, the unknown pathogen migrates through the olfactory epithelium to the olfactory bulb, finally entering the brain (45,46).

More recently, interest in the role of intestinal microbiota (symbiotic and pathogenic microorganisms residing in an environment) and the bidirectional gut-brain axis has increased. In PD, this biochemical signalling between the enteric and central nervous system appears to be disrupted by the intestinal microbiome (genetic material within the microbiota) (47). As with the case of the olfactory bulb, environmental factors such as exposure to pesticides, heavy metals intoxication, cigarette smoking or caffeine intake may change the composition of the microbiota (dysbiosis), thus increasing or reducing the risk of developing PD (48). In addition, there is compelling evidence suggesting a role of microbiota-derived intestinal inflammation as a pathogenic mechanism leading to PD (49).

It has been suggested that colonic biopsies looking for α-synuclein can be a reliable biomarker for prodromal PD (50,51). Nevertheless, recent studies have failed to show differences in α-synuclein staining in colon between subjects with PD and controls who underwent a routine colonoscopy for cancer screening (52,53). In addition, the oral and nasal microbiome has also been suggested as a potential biomarker (54), although more studies are needed.

Depression

The neuropsychiatric spectrum of symptoms is wide but depression stands out as a premotor symptom. Depression is common in the general population with an average prevalence of 13.5% (55), but prevalence in subjects with PD ranges between 30–45% depending on the clinical tool and study criteria (56,57). According to the Braak model, depression can be accounted as a complication of noradrenergic and serotoninergic deficits seen in the first stages of the disease (58). Unlike the other premotor symptoms previously discussed, depression lacks an objective method of measurement other than clinical rating scales. To improve the role of depression as a biomarker, other biomarkers to identify this symptom need to be developed (59).

Premotor Symptoms as Combined Biomarkers

Even though the premotor symptoms are more frequent in subjects with PD than in healthy subjects they are nonspecific. Consequently, a combination rather than the isolated symptoms may useful for diagnosing pre-motor PD (60). Aguirre-Mardones et al evaluated the perceived time of onset of other non-motor symptoms (hyposmia, constipation, and depression) in patients diagnosed with RBD. The three most frequent presentations were RBD followed by hyposmia; hyposmia followed by RBD; and hyposmia followed by RBD and constipation occurring at the same time span (61). In addition, Mahlknecht et al reported that olfactory dysfunction predicts an early phenoconversion from iRBD to a parkinsonian disorder (62). Mizutani et al showed that olfactory and cardiovascular sympathetic functions are correlatively impaired in early stages of PD (63), suggesting that degeneration of broad aspects of the cardiovascular sympathetic system occurs concurrently with olfactory system degeneration during the premotor phase of PD. In addition, Wu et al found that olfactory deficits were positively correlated with the occurrence of RBD and constipation (64); while Zhang et al showed that subjects with PD and RBD were more likely to report constipation in comparison to those with PD but no RBD (65).

The International Parkinson and Movement Disorder Society has recently developed research criteria for prodromal PD. These criteria include some nonmotor symptoms like RBD, olfactory loss, depression, and dysautonomia (constipation, hypotension, sexual and urinary dysfunction). Based on the likelihood ratios of each marker present for each subject, an estimate probability can be calculated (66). In example, a 50 year old male without any other markers

Table 3. Recommended clinical tools and gold standard to assess the main pre-motor symptoms

Pre-motor symptom	Screening tool	Gold standard
Rapid eye movement (REM) sleep behavior disorder	REM sleep behaviour disorder screening questionnaire (RSBDSQ)	Overnight polysomnography
Hyposmia	Self-administered odor questionnaire	Smell Identification Tests
Constipation	No scales or questionnaires recommendedUse Rome III criteria	Colon transit study
Depression	Geriatric Depression Scale (GDS-15) Hamilton Depression Rating Scale (HAMD-17) Montgomery-Asberg Depression Scale (MADRS)	Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria

has a probability of 0.4% for developing PD. If the same subject has confirmed RBD, hyposmia, depression and constipation, his risk of developing PD increases to 99%.

In summary, premotor symptoms are not only frequent in PD but also tend to cluster and have proven to be of diagnostic value.

Future of PD Diagnosis

Clinically, PD cannot be diagnosed until motor symptoms are present but based on the framework described in the preceding sections, it can be argued that subjects with PD, or at least with premotor PD, are seen first by a otorhinolaryngologist, sleep disorders specialist, gastroenterologist, internist or psychiatrist. At least theoretically, these specialists could diagnose subjects at risk of developing motor PD years or even decades before the typical motor symptoms associated with this disease appear. Besides a change in the paradigm and understanding of the disease, there are other issues to be solved in this matter.

For instance, some of the premotor symptoms discussed may not be recognized by the patient as a problem. It has been reported that 44% of the patients are not aware of their dream-enactment behaviors (67). Similarly, objective intestinal dysfunction as assessed by colonic transit time is considerably more prevalent than subjective constipation symptoms in subjects with PD (79 vs. 38%) (68). The same holds true for depression, where up to 61% of PD patients screening positive for depression on self-report were not recognized by neurologists on standard evaluation (69). As a consequence, specialists will require to assess for the presence of other premotor symptoms even if they appear to be unrelated to the main cause of consultation.

While it has been suggested to generally disclose the neurodegenerative risk to patients with idiopathic RBD (70), important ethical issues are clearly present. On one hand, currently there is no proven disease-modifying or neuroprotective therapy for PD. On the other hand, diagnosing subjects with premotor or prodromal PD is required to develop and conduct clinical trials aimed to modify the disease.

In addition, RBD is relatively infrequent and strongly associated with a risk of PD, but the frequency and strength of association is lower for the other symptoms. There is currently no recommendation on this regard, but it may be suggested that RBD and hyposmia confer a higher risk than constipation and depression. Consequently, patients with RBD and/or hyposmia should be routinarly screened for depression and constipation, as well as for subtle motor symptoms.

While specialists other than neurologists lack training or expertise regarding identifying, there are several clinical tools that can aid as screening tools for RBD (71), hyposmia (72), constipation (73) and depression (74) (Table 3).

Conclusions

The recognition of non-motor features, especially those which are present before the motor onset, may allow the diagnosis to be made earlier in the course of the disease granting a better quality of life. To achieve this, a multidisciplinary team involving different specialists is essential. Even though no proven neuroprotective treatment is currently available, it is expected that in the near future that premotor diagnosis of PD will be required for conducting such clinical trials. Movement disorders specialists and general neurologists have the responsibility of teaching current and future doctors that PD is no longer a disease of the brain, but a multisystem entity that begins with symptoms like hyposmia, constipation, depression and sleep disorders.

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