

Non-motor signs in Parkinson's disease: a review

Sinais não motores na doença de Parkinson: uma revisão

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ABSTRACT

During the past decade the view of Parkinson's disease (PD) as a motor disorder has changed significantly and currently it is recognized as a multisystem process with diverse non-motor signs (NMS). In addition to been extremely common, these NMS play a major role in undermining functionality and quality of life. On the other hand, NMS are under recognized by physicians and neglected by patients. Here, we review the most common NMS in PD, including cognitive, psychiatric, sleep, metabolic, and sensory disturbances, discuss the current knowledge from biological, epidemiological, clinical, and prognostic standpoints, highlighting the need for early recognition and management.

Keywords: Parkinson's disease, non-motor signs, dementia, hyposmia, psychosis.

RESUMO

No decorrer da última década, a visão da doença de Parkinson (DP) como um distúrbio de movimento puro mudou significativamente, sendo atualmente reconhecida como um processo multisistêmico com diversos sinais não motores (SNM). Além de serem extremamente comuns, estes SNM têm um impacto muito significativo na limitação funcional e da qualidade de vida na DP. Por outro lado, os SNM são mal reconhecidos pelos clínicos e negligenciados pelos pacientes. Nessa revisão os SNM mais comuns na DP foram detalhados, incluindo distúrbios cognitivos, psiquiátricos, do sono, metabólicos, e sensitivos; e discutindo o conhecimento atual sob o ponto de vista biológico, epidemiológico, clínico e prognóstico, destacando a necessidade de reconhecimento e abordagem terapêutica precoces.

Palavras-chave: doença de Parkinson, sinais não-motores, demência, hiposmia, psicose.

The traditional pathological description of PD as a pre-synaptic degenerative process affecting dopaminergic neurons in the substantia nigra pars compacta (SNc) of the midbrain with formation of Lewy bodies (LB) has changed dramatically in the last decade since functional and neuropathological studies showed the occurrence of extensive extranigral involvement¹. Among these investigations, the seminal study of Braak et al.² suggested that the degenerative process in the PD starts in the caudal regions of the brainstem and the olfactory bulb, progressing in the caudal-rostral direction. The involvement of the SNc occurs, according to this hypothesis, on the third of a six-stage process that begins in the dorsal motor nuclei of the glossopharyngeal and vagus nerves and the olfactory bulb. Although it demonstrates the occurrence of this peculiar pathological distribution, the study fails to make the clinical correlation between any of these changes and motor or non-motor manifestations. On the other hand, even considering this

caveat, it was one of the studies that formed the basis and motivated the dissemination of the concept of the existence of non-motor signs (NMS), especially dysautonomia, olfaction and sleep disorders, as part of the disease, sometimes even preceding the classic motor symptoms of PD.

The motor aspects of PD typically have a slow progression and direct correlation with the presence of neuronal degeneration in the SNc, but they do not represent the actual beginning of the degenerative process. This process is, in fact, in full progression, despite been apparently silent when one seeks only for motor signs³.

EXTRANIGRAL DEGENERATION

The notion of PD as a multisystemic disease, not restricted to the nigrostriatal tract is not new, however the cited

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study of Braak et al.² not only showed that the degenerative process begins in non-dopaminergic structures of the brain stem, or even in the peripheral autonomic system, but also influenced the way in which we interpret apparently nonspecific signs that can be detected in the course of the disease. Another innovative aspect of this hypothesis is that the disease process advances in a sequential and predictable manner. Thus, when the process affects the SNc, components of other brainstem structures are already heavily affected. Also, from the moment when the motor signs appear, other brainstem nuclei will also degenerate, until finally the degenerative process reaches the anteromedial temporal cortex and then the neo cortex, starting with associative and pre frontal, until finally sensory, motor and pre motor areas are affected.

This concept, however, does not escape criticism and between 6% and 43% of the cases described in other pathological studies published since then do not fit perfectly with this model, especially the sequential aspect⁴. For example, a study that evaluated pathologically confirmed cases of PD with the intention of testing the Braak's model, showed that the distribution of the pathological markers is consistent with this pattern, but also showed that the pathologic density in the brainstem was different from the cortex, indicating that the accumulation of degeneration occurs in these two regions independently. Another important point was the lack of an adequate correlation between the clinical and pathological findings in terms of duration and severity of motor and NMS and between neuronal loss density and these same clinical variables⁵. Finally, almost 10% of cases from other pathological series feature the degenerative process markers in the midbrain and cortex, but not in the most caudal areas of the brainstem, contrary to the model of an upward progression from the medulla.

Regardless of the lack of consonance of pathological studies in PD, especially in terms of its dynamic distribution during the course of the disease, the literature is unanimous in regards to its progressive and diffuse distribution, advancing in either phase of the disease to cortical and subcortical areas, not restricted to the motor system.

PREVALENCE AND IMPACT OF NON-MOTOR SIGNS OF PARKINSON'S DISEASE

Most, if not all, patients with PD present NMS. A survey that included 1,072 patients with PD using a structured questionnaire conducted in Italy showed that 98.6% of patients had at least one of the SNM studied, including more commonly psychiatric, sensory and sleep-related symptoms. On average, in this study, each patient had about eight symptoms, a figure that increased according to the duration of the disease and its severity⁶. These NMS can occur at any time in the course of the disease, however some are generally described in the early stages, such as REM sleep behavior

disorder (RBD), olfactory disorders and constipation. Others tend to occur in the later stages, such as psychosis and cognitive deficits. A third group of these symptoms do not have a clear relationship with stages of the disease, including depression and forms of dysautonomia⁷.

The functional and the quality of life (QoL) related impact of NMS is very significant, equaling or even surpassing those imposed by common motor symptoms of PD. A comprehensive review of the literature assessing the main determinants of QoL in PD showed that this parameter tends to deteriorate in the later stages; however it does not correlate closely with disease duration and clinical assessment scores. On the other hand, the presence and severity of symptoms of depression, cognitive impairment and sleep problems have a strong correlation with QoL scores. This review also showed that in half of the studies, the main limitation of QoL was a NMS, similar to the motor signs classically considered refractory and disabling such as postural instability and gait disorders⁸. From a different perspective, a study that evaluated the main limiting factors of activities of daily living (ADL) in patients undergoing stereotactic surgery with deep brain stimulation for the treatment of PD, showed that after nine years since the intervention, non-axial signs, including tremor, rigidity and bradykinesia, remained relatively stable. However, axial signs (postural instability and gait disorder) and NMS began to exert a growing negative effect, reflecting levels of functionality that were similar or worse than those observed before surgery⁹.

NMS represent some of the leading causes of disability and impairment in QoL in PD, therefore, the recognition of these aspects of the disease is essential to provide care that can potentially induce a decisive and comprehensive impact in these cases¹⁰. Despite its importance and frequency, NMS are not adequately recognized in clinical practice. The impact and the ability to detect NMS in specialized consultations were the focus of the study by Gallagher et al.¹¹ that evaluated cases divided into those with advanced disease and another group with a confirmed diagnosis of PD for less than least five years, which was considered "recent diagnosis". In both situations the NMS were common and associated with limitations in QoL that surpassed those caused by motor dysfunction. Interestingly, the NMS with the greatest impact were the same in both groups: autonomic dysfunction and fatigue, added by depression for the group with more recent diagnosis. The ability to detect NMS is not uniform. In part this is due to the perception that certain NMS are not directly related to the DP, such as apathy and sphincter dysfunctions, so patients do not spontaneously report and the complaints can be missed during routine clinical investigations. Depression and hallucinations appear to be routinely investigated in some studies but not in others¹¹. Most studies evaluating the ability to detect NMS compare the clinical documentation of consultations with results of specific questionnaires that were not designed and validated instruments to be used by the clinician on a daily basis. Thus, other

explanations for these differences are the presence of false-positive responses to the questionnaires, lack of hope for the resolution of problems in spite of motor symptoms that are considered “legitimate” neurological, and insufficient time for consultation.

Another study analyzed the results of a series of scales and NMS-related questionnaires compared to the chance of identifying these same signs by the neurologist who treated the patient with PD. This study showed that depression, anxiety, fatigue, and sleep disturbances are not identified in almost 50% of visits¹². A study with similar methodology assessed which were the NMS observed in PD patients among the ones listed in a specific questionnaire compared to those cited by the same patients during a specialized routine medical consultation. Almost 43% of NMS noted in the questionnaire had not been mentioned in the consultation, including hallucinations, sleep disorders (insomnia and RBD), drooling and restless legs syndrome. The authors highlight that from the list of non-declared NMS, most were potentially treatable. This study also found more NMS among patients with the rigid akinetic form of PD¹³. A study involving cases with pathological confirmation of PD retrospectively seeking the first signs of the disease, showed that nearly a quarter of the patients had NMS in the early stages and that the presence of such symptoms led to a greater chance of demand for orthopedic surgeons and rheumatologists than neurologists¹⁴.

CLINICAL CHARACTERIZATION OF NON-MOTOR SIGNS IN PARKINSON'S DISEASE

We discuss below a few key points about each individual NMS. Autonomic dysfunction also comprehends an important and broad group of NMS that is not included in this review (except for constipation) due to length restrictions and also because we believe this particular topic deserves a review on its own.

A summary of prevalence, its correlation with disease progression, level of functional disability and potential role as premotor signs of PD is presented in Table 1 and Figure.

Olfactory deficit

The first description of olfactory deficits in PD was made almost 40 years ago¹⁵ and five years later this signal was described as an early feature and a “precursor of motor signs”¹⁶. During the 80s, studies have shown that discrimination, detection threshold, and identification of odors are abnormal in PD^{17,18}. In addition, sequential studies have shown that olfactory deficits in these cases do not depend on odor subtype, age of onset, duration and severity of the disease, motor laterality and phenotype, treatment, and presence of cognitive impairment^{19,20}. Finally, a more recent study showed that hyposmia does not fluctuate during periods on and off²¹. The

Table 1. Non-motor signs: prevalence, respective level of functional disability and potential role as premotor signs of Parkinson's disease^{15,16,17,18,19,35,43,44,45,47,48,49,51,52,53,60}.

	Prevalence* (%)	Disability	PMS
Hyposmia	50-75	+	+
RBD	42-58	++	+
Depression	35-68	++++	-**
Constipation	50-79	++	+
Weight loss***	21-30	+	+
Dementia	48-78	++++	-
Psychosis	50-80	+++	-

PMS: Pre motor sign; RBD: REM sleep behavior disorder. *Life time prevalence; **Probably a pre morbid risk factor, not a PMS; ***Mild/moderate weight loss has been documented as a PMS. Prevalence figures represent undernutrition.

combination of these data indicates that this dysfunction is not directly related to the dopaminergic dysfunction or with the degenerative process responsible for motor signals of PD. In fact, a study that evaluated cholinergic and dopaminergic innervation concluded that the cholinergic deficit, especially located in the limbic cortex, represents a more robust determinant to olfactory deficits in PD than nigrostriatal dopaminergic denervation²².

From a pathophysiological point of view, the presence of LB in the olfactory bulb seems to be a constant finding in patients with symptomatic PD, occurring in 100% of cases examined post-mortem. Congruent with the hypothesis described by Braak et al.² cited previously, which proposes that the degenerative process in PD also begins in the olfactory bulb and anterior olfactory nuclei, loss of olfactory sensitivity occurs in 70%-90% of patients with PD, including newly diagnosed cases who did not yet receive any form of treatment²³. Besides being an inherent part of the established disease, several evidences suggested and consolidated the hypothesis that hyposmia is an early sign of pre-motor DP, starting with the fact that the presence of LB in the SNc invariably accompanied these pathological markers in the olfactory structures. The opposite, however, is not always true, i.e., many cases have LB in the olfactory bulb with intact SNc. The length of time between the expression of hyposmia and the appearance of motor signs is still unknown and may be of several years²⁴.

Since the early 1990s, it was demonstrated that olfactory deficits could distinguish sporadic PD from essential tremor, dystonic tremor and progressive supranuclear palsy (PSP)²⁵. Later, this same conclusion was determined with respect to multiple system atrophy (MSA), cortico basal degeneration and monogenic parkinsonism related to mutations in the PINK1 and PARK2 genes^{26,27} while cases with mutations in the LRRK2 gene have intermediate results^{28,29}.

The main longitudinal study showing that the olfactory deficit may precede PD was held in Honolulu, Hawaii, by the group of Ross et al.³⁰ who published a series of articles showing that in the longitudinal follow-up of more than 2,000 neurologically

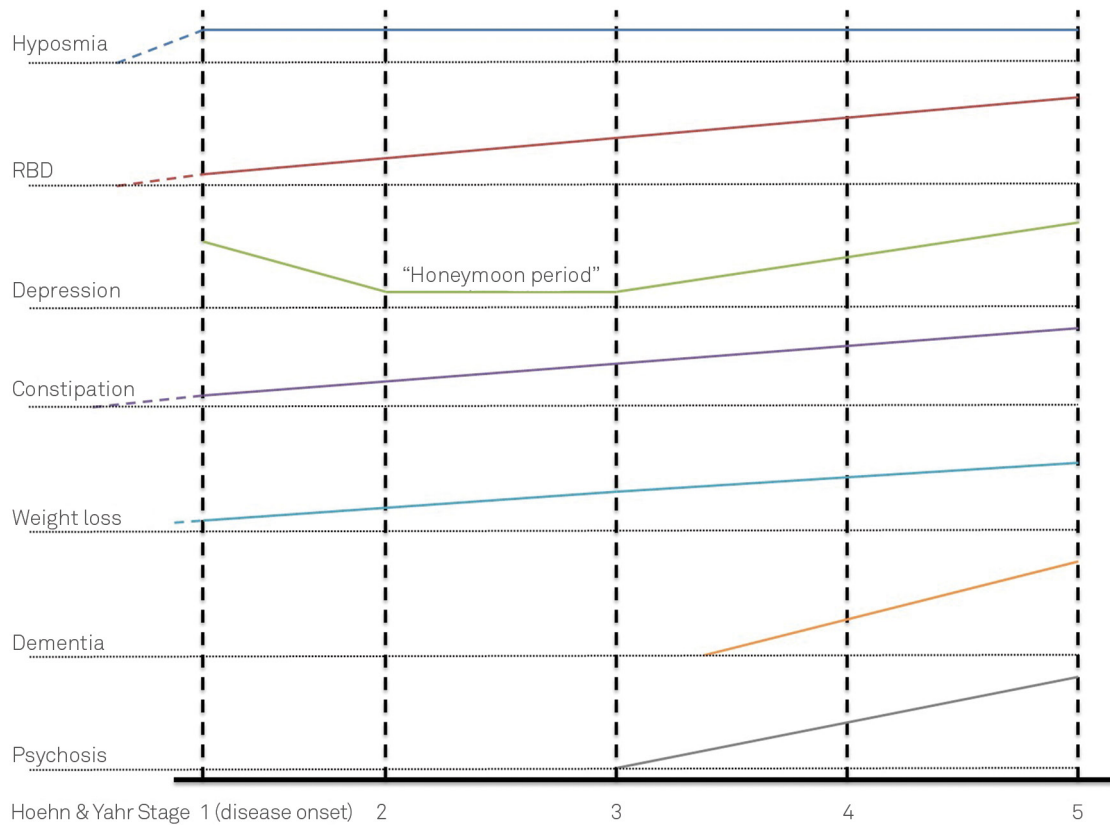


Figure. Progression of non-motor symptoms throughout disease stages in Parkinson's disease.

healthy elderly individuals, those with proven olfactory deficit had a higher risk of developing symptomatic PD clinical and when they remained asymptomatic, these individuals presented LB in the SNc on post-mortem examination. Other studies that strengthen the idea that the olfactory disorder precedes the motor onset of PD include those by Berendse et al.³¹, and its follow-up after three years³² showing the development of PD signals in cases of a group of “high risk”, which included family members of patients with PD who had hyposmia, while family members without hyposmia remained asymptomatic after two years. Finally, a study that evaluated possible associations between olfactory deficit and the risk of developing dementia in PD with an observation period of three years using functional imaging techniques showed that changes in the areas associated with olfactory function have a close relationship with cognitive decline. In addition, the study also showed that more severe hyposmia represents a prominent factor for the development of dementia³³.

REM sleep behavior disorder

Physiologically, patterned changes of neuronal activation and release of specific neurotransmitters in the brain stem occur during the REM sleep phase, inducing, among other phenomena, motor inhibition and muscle atonia. RBD is a parasomnia characterized by the loss of this normal muscle atonia during this sleep stage³⁴.

The gold standard for diagnosis requires polysomnography demonstrating excessive muscle activity, continued or intermittent tone of submentonian during REM sleep³⁵. Clinically, the diagnosis can also be established using historical data using instruments that range from formal criteria of the Manual of Disorders of Sleep of the American Academy of Sleep Medicine³⁶ to the use of a single question with a categorical “yes or no” type answer³⁷. The typical clinical picture includes a description of movements associated with dream content and aggressive behavior with interpretation of such contents. Since the dream content in these cases tends to involve conflict situations, there is usually sleep disruption of patients and/or their bed partner, who are occasionally victims to physical harm, including descriptions of trauma with significant severity³⁵. Patients with PD and RBD probably have a different distribution of the degenerative process compared to those without this parasomnia, once it's the most probable substrate involves the pons tegmentum and the medial nuclei of the medulla³⁸. Clinically, RBD may be linked to particular manifestations such as worse scores of postural instability and gait, lower amplitude of motor response to levodopa, higher frequency of orthostatic hypotension and visual color perception deficit. From a behavioral point of view, RBD is associated with vivid dreams and visual hallucinations, and is a warning sign for the occurrence of dementia and other

cognitive deficits involving specific episodic verbal memory, executive functions and visuospatial and visuoperceptual processing³⁵.

Interestingly, a study that analyzed the quality of the movements during episodes of RBD showed that they do not have the standard asymmetric signs of parkinsonism observed during wakefulness, and are rapid, large, coordinated and symmetrical, however violent, ballistic and occasionally repetitive, suggesting that during REM sleep there may be a transient re-establishment of more physiological basal ganglia function. Alternatively, parkinsonism may disappear during REM sleep because at this stage the movements generated follow directly to pyramidal tract neurons and sequentially to the peripheral motor neuron, bypassing the extrapyramidal system and the physiological barrier responsible for atonia during this sleep stage in the brainstem³⁹.

RBD occurs in up to half of PD patients and, as in the case of hyposmia, is considered an established pre-motor symptom. Also, in almost half of PD patients and RBD, the sleep complication precedes the onset of parkinsonism by several years. The mean interval from the onset of symptoms of RBD and motor signs is 11 to 12 years, but may range from 1 to up to 20³⁵. Moreover, cases of apparently idiopathic RBD are uncommon and have a chance of more than 50% to develop neurodegenerative diseases after 12 years of follow up, including more commonly PD, followed by LB dementia, Alzheimer's disease and MSA⁴⁰. Another important aspect is that individuals with idiopathic RBD with the highest chance of developing PD have peculiar sleep characteristics, including higher proportion of REM sleep, more periodic lower limb movements per hour during of non-REM sleep and abnormal intensity of muscle atonia⁴¹. Finally, although RBD is described in atypical forms of parkinsonism associated with the pathological background of synucleinopathies, particularly multiple system atrophy and LB dementia, their occurrence in PSP, although less common, is significant, indicating the concept that this parasomnia is not related to a specific molecular form, but rather to a specific topographic progression of the degenerative process⁴².

Behavioral disorders

Mood disorders are common in PD, occurring in more than a quarter of newly diagnosed cases. Several studies have also shown that individuals with depression are 2.2 to 3.2 times more likely to develop PD compared to healthy controls⁴³. Although the available data regarding this correlation are less conclusive than for hyposmia and RBD, the onset of depressive symptoms may precede the motor signs, with a peak around 3-6 years before the diagnosis of PD. One of these studies evaluated 1,358 patients with depression and 67,570 healthy individuals matched for age and sex for an average period of 15 years, showing a chance of occurrence of PD in those with a history of depression 13.3 times higher than controls without depression. Another epidemiological

study found similar results with a chance of 2.95 times for the occurrence of PD in individuals with depression. In these studies and in the literature in general, depression is considered a risk factor, as well as family history and life in a rural environment, but not necessarily a pre-motor symptom⁴⁴.

In the course of the disease, depression is one of the major indicators of a poor quality of life and functional disability, occurring in about 40% of patients in cross-sectional studies and almost 70% in longitudinal studies⁸. The diagnosis of depression in PD may be complex because some of the signs of the disease itself may mimic it. Moreover, there are peculiar aspects regarding the presence and severity of depressive symptoms compared to the general population with depression (Table 2) PD depression tends to manifest with more intense anxiety, pessimism, hopelessness, social withdrawal, self-depreciative thoughts, and introversion, but, on the other hand, less felling of guilt, ideation of death and suicide⁸.

Depression in PD is probably multifactorial, involving a neurobiological substrate permeated by evidence of a reactive component related to living with a chronic neurodegenerative disease and its complications and limitations. For example, a study by Rickards et al.⁴⁵ showed that the frequency of depression is high in the early stages of PD, when the patient is diagnosed, decreasing when starting treatment, reflecting the classic "honeymoon phase", and increasing again with the progression of symptoms in later stages. In addition, depression in PD is directly related to the severity of motor symptoms and may fluctuate along with motor fluctuations, reflecting the pharmacological effect of levodopa. The biological basis of depression also has a pathological basis, related to the presence of PD's own degeneration markers in serotonergic and noradrenergic structures as the raphe nuclei and limbic structures⁸.

Still under the behavioral aspect, a premorbid personality in PD has been observed, including a relatively uniform description that often uses terms such as introversion,

Table 2. Clinical differentials in presentation of depression in Parkinson's disease (PD) versus the general population.

More common in PD depression
Apathy
Dysphoria
Irritability
Anxiety
Fluctuation of mood throughout the day
Pessimism
Hopelessness
Social withdrawal
Introversion
Self-deprecating thoughts
Uncommon in PD depression
Sensation of guilt
Self punishment
Death ideation
Suicide

behavioral inflexibility, difficulty with abstraction thought, more reliability, responsibility, loyalty, subordination, less tendency to leadership, conservative attitude with self-protection, intense self-control and difficulty expressing aggression. Unfortunately, these aspects are all very common in the general population and have a low specificity for PD⁴⁶.

Constipation

The clinical history of constipation is common at diagnosis in cases of PD, and is also described before the emergence of motor signs. As a pre-motor symptom, it was described in a variable period that can reach up to 24 years before the onset of parkinsonism in studies using different methodologies. In a longitudinal study of 6,790 males with constipation, the risk of occurrence of PD was 2.7 times higher than in those without this symptom. In this study, the mean time interval between the detection of constipation to diagnosis of PD was 12 years, ranging from two months to 24 years⁴⁷.

The pathological support of this relationship comes from the observation that 9% to 17% of healthy subjects have alpha synuclein aggregates in the peripheral autonomic system, including abdominal-pelvic, cardiac and myenteric plexus of the esophagus, sympathetic ganglia and vagus nerve. Thus, from the pathophysiological point of view, constipation may reflect not only this peripheral involvement but also central mechanisms that cause pelvic floor dysfunction. Some of these individuals with peripheral autonomic disorder still present LB in the central nervous system and others have other pre-motor signs such as RBD, striatal abnormalities in functional tests or even pre-diagnostic PD as described above, in another words, the presence of a subtle cardinal sign that did not fill formal criteria for PD^{47,48}.

Weight loss

Several studies have found that PD patients have lower body mass index (BMI), compared to healthy controls matched for sex and age. The etiology seems to be multifactorial, related to the presence of dyskinesias, change in eating habits, effect of medication (mainly levodopa), longer time for the ingestion of meals leading to lower energy intake and earlier satiety, in addition to being potentially related to intrinsic physiological changes of the neurodegenerative process. For example, the concentration of leptin, insulin-like growth factor type 1 (IGF-1), and thyroid-stimulating hormone were investigated in patients with PD and weight loss compared to controls with PD but no weight loss, finding lower levels of leptin and higher IGF-1 in the study group^{49,50}.

The onset of weight loss in PD does not have a defined correlation with the stages of the disease, and may be an early expression or even precede the onset of motor signs. A prospective study that examined the changes in BMI in 468 patients with PD using anthropometric data collected before the onset of motor symptoms, followed during the course of the disease showed that the average body mass remained

stable in most subjects up to a variable period before the onset of motor signs. This period ranged from a few months up to four years. Interestingly, this study showed a tendency to the increase in caloric intake while the BMI decreased. In the course of the disease, the reduction of BMI followed a continuous process with the same tendency of the pre-motor period, indicating that, regardless of the process that triggers this early change in BMI, it is relatively uniform and follows the disease progression⁵¹.

Cognitive deficit

Several degrees of cognitive impairment are common features of PD and, considering the model of disease progression described by Braak, may be a natural consequence of end-stage disease². The diagnosis of dementia is also especially common in PD, It has been described in about 20% of PD cases in cross-sectional studies⁵², and almost 80% in longitudinal studies, with an incidence at least four times greater than in the general population⁵³. Furthermore, despite being more common and severe in the later stages, cognitive impairment that does not cause enough dysfunction to fulfill diagnostic criteria for dementia may be present early in the course of the disease, with abnormalities in neuropsychological tests detected in up to 24% of patients at diagnosis of PD. Finally, those with the formal diagnosis of dementia will present it for an average period of four years during the course of the disease⁵³.

Cognitive disorders tend to exacerbate the motor symptoms disabilities in PD. In fact, the presence of cognitive impairment or dementia in PD patients is associated with loss of independence, poor quality of life and shortening of lifespan. Moreover, individuals in advanced stages of PD who develop dementia, often present a functional decline that follows a stereotyped pattern, indicating that the beginning of this sign announces the need for a more intensive care and increased risk of mortality⁵⁴. Thus, the onset and progression of cognitive impairment in PD have an important influence on patient management and prognosis.

The phenomenology of specific cognitive symptoms associated with PD varies and probably reflects the heterogeneous underlying neuropathological substrate. The most common cognitive impairments are attention, executive behavior and visuospatial processing deficits, although patients may also exhibit different degrees of loss of memory, which could be, in some cases, a dysfunction secondary to a frontal (i.e., executive behavior) rescue information. In the same way, dementia in PD is not characterized by an intrinsic deficit of language, but may be associated with difficulty in processing and composition of phrases, which are also executive dysfunctions⁵³. Some lines of research suggest that the executive impairments in PD are an early signal due to changes in dopaminergic stimulation in the frontal cortex, whereas impairments in semantic memory and visuospatial working correspond to the posterior neuropathological involvement of temporal and parietal cortex, conferring a higher risk of dementia in PD⁵³.

Among the risk factors for dementia in PD, age is the most important. On the other hand, the increased age-related dementia risk does not seem to be associated with the possible influence of age of onset of motor symptoms; in other words, patients develop dementia in a similar mean age, regardless of when the motor signs appear⁵⁴. Other studies also showed that cognitive impairment in PD correlates with the severity of motor disabilities, male gender, low education, visual hallucinations and the presence of rigidity and axial bradykinesia⁵⁵.

The pathological basis for dementia in PD is, in part, related to the spread of LB to the cortex, which occurs in the later stages of disease². Moreover, other studies show that the pathology of the cognitive impairment in PD is probably multifactorial, including LB and pathology characteristic of Alzheimer's disease, along with factors related to age and other comorbidities⁵⁵.

The effect of treatment must also be considered, since pharmacological and non-pharmacological interventions could worsen incipient cognitive impairment. The use of anticholinergics, for example, classically enhances the cognitive symptoms of PD, as well as treatment with deep brain stimulation. In these cases, although the motor function has a good response to surgery, quality of life tends to decline after the first 6 months, probably, in part because of cognitive decline, which seems to be more significant when the target of this intervention is the subthalamic nucleus⁵⁶.

Psychosis

Psychotic symptoms such as hallucinations and delusions are common in PD patients and occur from 10% to 80% of cases, depending on the definition and the studied population. Risk factors includes cognitive impairment, dementia, age greater than 65 years, advanced disease, longer duration, presence of sleep disorders, depression, visual disturbances and use of most of the drugs needed to treat motor symptoms of PD, the commonest culprits been dopamine agonists,

levodopa, amantadine and anticholinergics⁵⁷. Psychosis is associated with different pathological and molecular abnormalities, however the most consistent findings suggest the presence of LB in the temporal/limbic cortex⁵⁸.

Diagnostic criteria include the presence of one of the following symptoms: illusions, false sense of presence, hallucinations and delusions in the context of previous diagnosis of PD defined by Queen Square Brain Bank criteria. In addition, symptoms should be recurrent or continuous for at least one month⁵⁹ visual hallucinations tend to be more common, including a wide range of imagery, from simple indiscriminate shapes to well-formed entities with complex interaction with patients. Auditory hallucinations and other sensory functions are less common⁶⁰.

As mentioned before, psychotic symptoms are more frequent in patients with cognitive impairment. In the case of a subclinical deficit, the presence of psychosis must be considered as a predictor of imminent cognitive decompensation and dementia. Thus, the so-called "benign" hallucinations are actually part of a gradual process with a potentially malignant prognosis⁶⁰.

FINAL REMARKS

Despite the former cited observations about the functional and QoL related impact of NMS, until recently they received relatively little attention from clinicians. In part, that has happened due to unawareness and difficulties in conducting a more thorough and extensive assessment in a system that has limits of time and resources. Moreover, many patients and their caregivers tend to interpret NMS as being not "parkinsonian", not deserving evaluation by a specialist in neurological diseases. On the other hand, our review shows that most of the NMS that have a significant impact on QoL and functionality are, at least in part, manageable and should be properly and promptly identified.

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