Systematic review of early loss of dopamine expressed in non-motor symptoms of Parkinson’s disease

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**Summary**

**Background and aim:** The diagnostic value of the presentation of non-motor symptoms (NMS) in Parkinson’s disease (PD) remains unclear. These symptoms are significant in primary health care diagnosis predicting accurately the time at which deterioration of quality of life begins, the caregiver burden, and lastly the mortality. Diagnosis of NMS is not always straightforward. The aim of this review is to critically analyze and summarize the clinical literature focusing on a possible common presentation to facilitate its early diagnosis, control and treatment.

**Materials and methods:** The Medline (PubMed), Cochrane Central Register of Controlled Trials, The Wiley Library and Oxford University Press Journals Collection databases were searched electronically for studies published in the last 20 years (1998–2018) using keywords including the different well known non-motor symptoms in early Parkinson’s disease. In addition to other studies that demonstrate the importance of NMS to predict the disease course.

**Results:** A total of 150 articles were found during the initial search; 51 were deemed suitable for this review. Among them were the Cohort studies, case studies, metanalyses and reviews that were cautiously analyzed and commented.

**Conclusions:** Although the information gathered about the premorbid symptoms of PD these last 10 years has increased, there is still a lack of awareness in health care. It is crucial to educate and update professionals on these symptoms.
Abbreviations list

NMS - Non motor symptoms
PD - Parkinson’s disease
PARS - Parkinson’s associated risk syndrome
RBD - rapid eye movement sleep behavior disorder
IRBD - Idiopathic REM sleep behavior disorder
HC - healthy controls
MSA - multiple system atrophy
PSP - progressive supranuclear palsy
APD - atypical parkinsonian disorders
OF - olfactory function
DAT - Dopamine Transporter-deficiency imagine
UPDR - Unified Parkinson’s Disease Rating Scale
PSG - polysomnographic
GDS-15 - The Geriatric Depression Scale
BDI - Beck Depression Inventory
MADRS - Montgomery-Asberg Depression Rating Scale
Terms

- **Unified Parkinson’s Disease Rating Scale (UPDR):** comprehensive 50 question assessment of both motor and non-motor symptoms associated with Parkinson’s. UPDRS features sections require independent completion by people affected by Parkinson's and their carers, and sections to be completed by the clinician.
  - Part 1: non-motor experiences of daily living
  - Part 2: motor experiences of daily living
  - Part 3: motor examination
  - Part 4: motor complications
  (Goetz et al 2008)

- **The Geriatric Depression Scale (GDS-15):** is a self-report measure of depression in older adults. Users respond in a “Yes/No” format. These 15 items were chosen because of their high correlation with depressive symptoms in previous validation studies.
  (Sheikh & Yesavage, 1986)

- **The Beck Depression Inventory (BDI):** is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression. The BDI takes approximately 10 minutes to complete, patients require a fifth – sixth grade reading level to adequately understand the questions.
  (Beck, et al., 1961)

- **The Montgomery-Asberg Depression Rating Scale (MADRS):** is a 10-item clinician-administered scale, designed to be particularly sensitive to antidepressant treatment effects in patients with major depression.
1. Introduction.

Parkinson’s disease is the second most common neurodegenerative disease worldwide. Diagnosis of PD relies on the identification of the classical motor symptoms incorporated into clinical diagnostic criteria. Nonetheless, at least 50% of the nigrostriatal neurons have been lost at the time of diagnosis and other pathological abnormalities are thought to start in some brain regions earlier than nigrostriatal degeneration.[1]

Parkinson’s associated risk syndrome (PARS) individuals may have genetic risk factors or subtle, early non-motor symptoms that occur before the onset of typical motor symptoms including abnormalities in olfaction, constipation, cardiac imaging, vision, depression, fatigue and cognition. [2]

The investigation of all these clinical biomarkers appearing previous to PD diagnosis during randomized clinical trials, case control studies and cohort studies enable the inclusion of improved prediagnostic strategies in primary health care. W. Le et al. remarked that “although clinicians and scientists are aware of the importance and necessity of an early diagnosis, to date, no confirmed biomarkers can be applied clinically for the accurate prediction of PD onset at the prodromal or preclinical phase. [7] Hence, there is an unmet need to exert more effort on the discovery and identification of specific biomarkers for the early diagnosis of PD.”

This systematic review gathers the most recent data of NMS of PD by the analysis of different types of studies obtained during the last 20 years focusing more on the earliest most common symptoms (hyposmia, rapid eye movement sleep behaviour disorder, constipation and depression). The inclusion of these results in models that combine more traits (age, gender, family history, and some motor symptoms) would dramatically increase the sensitivity and specificity of an early diagnosis.

Moreover, it can be stated that the investigation of the severity of clinical features of the prodromal and motor phases (directly correlated to the pathological changes in the central and autonomic nervous systems) would allow a sequential plan of disease progression in addition to a more exact prediction and prognosis. [3]
2. Discussion of the results

NMS can be broadly divided in the following categories: sensory features, neuropsychiatric and cognitive symptoms, sleep disorders, and autonomic dysfunction. In 2015 a conducted meta-analysis based on 332 publications obtained different prevalence of premotor symptoms in PD. These are the results of each NMS after PD diagnosis: **hyposmia** was the most prevalent (75.5% in cases vs. 19.1% in healthy controls), followed by **constipation** (50% vs. 17.7%), **anxiety** (39.9% vs. 19.1%), **rapid eye movement sleep behaviour disorder** (RBD) (37.0% vs. 7.0%), **depression** (36.6% vs. 14.9%), and excessive daytime sleepiness (33.9% vs. 10.5%). Despite the heterogeneous results across studies due to the different contributing factors, analyses revealed higher prevalence in future PD cases than in healthy controls (HC). [9] *(Figure No 1)*

![Figure No. 1. Prevalence of premotor NMS](image)

However these premotor symptoms are more frequent in subjects with PD than in healthy subjects they are still nonspecific. As Rodriguez-Violante et al. stated the combined results of the prevalent biomarkers rather than isolated symptoms may be more useful for diagnosing pre-motor PD. It could be suggested that RBD and hyposmia confirm a higher risk than constipation and depression and are also more infrequent and strongly associated with a
risk of PD. Consequently, patients with RBD and/or hyposmia should be routinely screened for depression and constipation, as well as for subtle motor symptoms.[10]

Aguirre-Mardones et al evaluated the perceived time of onset of hyposmia, constipation, and depression in patients diagnosed with RBD. The three most frequent associations were RBD followed by hyposmia; hyposmia followed by RBD; and hyposmia followed by RBD and constipation occurring at the same time span. Idiopathic REM sleep behavior disorder (IRBD) patients frequently exhibit NMS that occur in premotor PD, particularly hyposmia and constipation. In IRBD, the perceived timeline of NMS is highly variable. This variability may suggest that pathological changes occurring in IRBD subjects are also heterogeneous and not restricted to the structures that regulate REM sleep.[11]

In the light of the results regarding the prevalence of certain premotor pathological findings, the previously suggested are suspected to have the strongest evidence in the involvement of early diagnosis of PD while being the most useful for the investigation of premotor symptoms. This is the reason why they will be the NMS discussed (hyposmia, RBD, depression and constipation).

A. 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. A recent investigation of the prevalence of hyposmia at the time of diagnosis reported that 73% of PD patients experience smell disorders. It is common at the time of PD diagnosis and increases the risk of dementia up to ten years after diagnosis regardless of baseline cognitive function. [50] In the data about prevalence of hyposmia prior to diagnosis however, the differences between prior to PD diagnosis group and HC were smaller (35.5% in future PD cases and 17.4% in HC). [9]

One of the last studies on the matter proofed that normal olfactory function (OF) together with normal cognition at baseline of diagnosis predicts a benign cognitive course up to ten years after diagnosis. [13]

The Braak propagation model, determines that deposition of alpha-synuclein in the olfactory bulb is firstly observed at stage one. This was demonstrated in a recent study in 2016, the presence of alpha synuclein in the olfactory epithelium was seen in six of the eight PD pa-
tients included (two patients with PD without dementia, two patients with PD with mild cognitive impairment, four PD with dementia). [16]

The pathophysiology of this smell disorder in PD is based as well on the deposition of alpha-synuclein along neurons throughout the olfactory pathway apart from the epithelium. [17] It can be stated thus that staging the severity of hyposmia in early PD patients provides more information about the starting point of the disease, given that the olfactory system is one of the first areas affected by Lewy pathology. Worsening of OF reflects severe extranigral disease and therefore is associated with earlier cognitive impairment through cortical involvement. More pathological changes are also seen in other areas of the olfactory system, including the anterior olfactory nucleus, cortical nucleus of the amygdala, piriform cortex, olfactory tubercle, entorhinal cortex, and orbitofrontal cortex.[14]

Identifying hyposmia prior PD diagnosis could be a great tool to differentiate PD patients from other parkinsonian disorders. In 2017 a Cohort study assessed and compared the ability to identify odors in patients with PD, multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) as well as healthy controls (HC). PD patients performed significantly worse in olfactory testing than HC with a sensitivity and specificity, exceeding 95%; the diagnostic accuracy of olfactory function cut-off values in patients with MSA was 78.6%, in patients with PSP was 77.1%. It is fair to conclude that odor identification can be useful to discriminate PD from healthy individuals and atypical parkinsonian disorders (APD), particularly MSA patients. [13] A second study, however, has shown different diagnostic accuracies in discriminating PD from both HC and APDs regardless of disease duration or severity (sensitivity and specificity of approximately 80%) of the sniffing Sticks identification test. [48]

A similar study was performed in 2004, the OF in vascular parkinsonism was compared to the OF in Parkinson’s disease. The results of the reports resolved that most of the patients with vascular parkinsonism and without associated dementia conserved their sense of smell. [29] Underlying once more the specificity of OF testing and its significance in the differential diagnosis.

Impaired OF is very useful predicting PD being one of the earliest NMS, relatively easy and cheap. Incorporating imaging techniques as Dopamine Transporter-deficiency imagine (DAT) and clinical data or testing could as well facilitate the premorbid diagnosis of PD. A prodromal cohort study observed PARS individuals using DAT imaging to determine if the combination of smell identification testing followed by DAT imaging could accurately identify individuals from population at risk for conversion to a clinical diagnosis of PD. The results of
the study demonstrate that the combined assessment of hyposmia and DAT deficit can be highly predictive of conversion to PD within 4 years of clinical follow-up (67% of the patients with hyposmia and a DAT deficit converted to PD at 4 years). Lastly, individuals with hyposmia and a DAT deficit had a 5% reduction in DAT binding annually, which resembles the progression to early PD. [15]

Tests to determine hyposmia:

Clinical measurement and testing of olfactory performance usually focuses on three main attributes: olfactory detection threshold, odor discrimination and odor identification. However, M. E. Fullard et al exposes that the utility of an olfactory test in the clinical setting depends on four factors: its validity in the population being studied, reliability, ease of use, and cost. Because OF can be influenced by age, gender, and smoking status, it is important that normative data be available for a given test in order to accurately classify a patient’s olfactory impairment. [14] In 2010, a review was published about the tests that have been validated to evaluate OF in PD. They extracted the following data: [18]

<table>
<thead>
<tr>
<th>Test</th>
<th>Modality measured</th>
<th>Number of odors</th>
<th>Time to administer</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Pennsylvania Smell Identification Test</td>
<td>Odor identification</td>
<td>40</td>
<td>~15 min</td>
<td>Can be mailed to subjects and self-administered, well-validated, detects malingering, international versions available</td>
<td>Takes a long time to administer, Some batch-to-batch variation in odor strength</td>
</tr>
<tr>
<td>Brief Smell Identification Test</td>
<td>Odor identification</td>
<td>12</td>
<td>~5 min</td>
<td>Rapid, can be mailed to subjects and self-administered</td>
<td>Cannot detect malingering or differentiate subclasses of dysfunction</td>
</tr>
<tr>
<td>Smell Threshold Test</td>
<td>Odor detection threshold (multiple dilutions)</td>
<td>1</td>
<td>20 min</td>
<td>Well-validated</td>
<td>Expensive, takes a long time to administrate and requires a technician</td>
</tr>
<tr>
<td>Sniffin' Sticks®</td>
<td>Odor identification, discrimination and detection threshold</td>
<td>16</td>
<td>10–60 min (depending on whether all modalities or subsets are measured)</td>
<td>Well-validated, Can be reused for many subjects</td>
<td>Takes a long time to administrate and requires a technician</td>
</tr>
</tbody>
</table>

Figure No. 2
Comparison of psychophysical tests commonly used to assess OF in PD. Table extracted from [18]

B. Rapid eye movement sleep behavior disorder

RBD is a sleep disorder characterized by the patient physically acting out vivid dreams. They physically move limbs or even get up and engage in activities associated with waking. Some engage in sleep talking, shouting, screaming, hittting or punching. The dreams are
usually unpleasant and the acting out is frequently accompanied by vocal sounds and sudden, violent movements of the extremities.

Last data predicts the overall prevalence of RBD symptoms in PD as 23.6% compared to 3.4% in HC. [49] Although the prevalence prior to diagnosis is estimated in 17.9%. [9] Patients with diagnosed RBD are considered PARS individuals and so their follow up is a very valuable opportunity to observe the development of parkinsonism. A recent cohort study assessed 78 patients with idiopathic RBD (iRBD), during the study 20 developed parkinsonism. This cohort study assessed the motor symptoms before parkinsonism in iRBD individuals and controls, concluding that there is a prodromal interval of 4.5 years on the Unified Parkinson’s Disease Rating Scale (UPDR) for the PARS individuals before the detection of PD. The sensitivity and specificity 3 years before diagnosis was 71% and 82% using Purdue Pegboard and the alternate-tap test, parkinsonism being detected, whereas utilising a UPDR score >4 identified prodromal parkinsonism with 88% sensitivity and 94% specificity 2 years before diagnosis.[19]

On the other hand, some investigators evaluated and followed up the evolution of RBD in already diagnosed 113 early PD patients and a sample of HC. Compared to HC, polysomnographic (PSG) data of this long-term cohort of initially de novo PD patients shows a significant increase in the frequency of RBD in early PD over a time span of two years. The proportion of PD patients with RBD increased from 25% at baseline to 43% after two years (almost duplicating the baseline numbers). [27] This finding might be used to anticipate the progression of the disease.

To fully comprehend the pathogenesis of RBD in PD, it is essential to understand the histopathological changes in relation to the degeneration in the substantia nigra. REMS takes place only if balance between REMS on and off neurons or/and inhibitory and excitatory pathways exists. If these brain structures and their relationships suffer any degeneration this leads to RBD. French and Muthusamy explain this ethology based on the Braak description of the stage II of PD: Lewy body and neurite are formed in the sublaterodorsal nucleus, precoeruleus region, the magnocellular reticular formation, the dorsal raphe nuclei, and locus coeruleus. They begin to accumulate, thus threshold is reached and changes in sleep, behaviour and mood start to appear. [20]

The cognitive profile in PD patients presenting RBD was studied performing several cohorts during 2017. The results of the study concluded that RBD patients show a more impaired cognitive profile with higher mild cognitive impairment diagnosis frequency. This would ad-
vocate bigger neurodegeneration in the affected patients. [21] Relating the parallel progression of RBD in PD with the worsened cognitive functions. Lastly, RBD in PD patients has been associated to a rapid progression of nocturia as well. A case control proofed that patients that suffer RBD have a higher degree of worsening of daily activities and deterioration of quality of life. Therefore this relationship suggests a common pathophysiological mechanisms of their development, which include the structural changes in the brain stem nuclei previously mentioned. [22] However iRBD was associated with hyposmia, it is still controversial if this alliance of non motor symptoms could predict an outcome in future disease modification trials. After some research, the conclusion was not clear because the results in the studies were antagonising. [25], [26]

Test to determine RBD:

Notwithstanding in some population a well detailed sleep history may be enough to diagnose RBD, according to the selected data a definitive diagnosis can only be obtained with a PSG evaluation. The most significative recordings (due to its specificity in RBD) of the PSG would be the activity of the muscles of the chin and the flexor digitorum superficialis in the forearm. [23], [24]

C. Constipation

New studies demonstrated that constipation is one of the most pre-diagnostically present NMS in early PD patients. Constipation is a non-specific yet considered sensitive early symptom of PD with a sensitivity of 79% and specificity of 31% [12, 51]. It is as well emerging as one of the earliest features of autonomic dysfunction in Parkinson’s disease, developing as early as 15.3 years before motor features. [4]

However the etiologic mechanism of constipation in PD is not clear yet (it might be caused
by decreased neuronal density in the myenteric ganglion or phosphorylated alpha synuclein deposition in the colon walls), the detection of constipation during prodromal stages of PD can play an important role as a sensitive biomarker. [5]

In the last year, 2017, a Cohort study compared a sample of early PD patients to a healthy control group in order to assess the different prevalence between the groups of individuals. The results of the study corroborate that constipation has a higher prevalence in early PD patients than in healthy controls (32.4% vs 11.8%) at baseline. (“FIGURE 1.” Serra et. al) [6] Once again the prevalence prior to morbidity is different 20.0% vs. 9.3%. [9] This premorbid trait has been identified as the the most common autonomic complaint within the 2 years before Parkinson’s disease diagnosis. [8]

The latest theories take in consideration the gut’s flora as another potential factor for constipation and PD itself, a cohort connects the different microbiota of 76 PD patients, 21 iRBD patients (PARS), and 78 healthy controls. Its results reveal significant differences of gut microbial taxa in PD (particularly increased of Akkermansia sp.) and its prodrome iRBD in comparison to the healthy controls. Importantly as well the study revealed overlaps between PD and iRBD microbiota. This topic should be studied in more depth to accept or rule out hypothesis about how gut’s microbiome may be involved in the different stages of this eclectic disease. [28]

Diagnosis of constipation:

An international working committee recommended diagnostic criteria (Rome IV) for functional constipation. [47]

Rome IV stated that patients must experience the following symptoms in order to diagnose constipation:

A. Must include two or more of the following:
   - Straining during more than 25 percent of defecation.
   - Lumpy or hard stools (Bristol Stool Scale Form 1-2) in more than 25 percent of defecations
   - Sensation of incomplete evacuation for more than 25% of defecations.
   - Sensation of anorectal obstruction for more than 25% of defecations
   - Manual manoeuvres to facilitate more than 25 percent of defecations
   - Fewer than three spontaneous bowel movements per week

B. Loose stools are rarely present without the use of laxatives

C. There are insufficient criteria for irritable bowel syndrome.
D. Depression and mood disorders

There might be enough evidence that supports that depression in PD is not purely a consequent psychological reaction but it has biological basis. [33]

Depressive symptoms have been proven to be the most common psychiatric disorder and earliest to be detected in PD patients. [1] (see extracted “Table 3”)

Approximately 30–45% of PD patients are depressed, reducing both subjective and objective quality of life independently of motor deficits [44], in contrast to the general population which is roughly 13.5%. [45] The results of the prevalence prior to PD diagnosis and HC are different: 23.0% vs. 14.9%. [9]

In APD cases (including PSP, Corticobasal Degeneration, MSA and Dementia with Lewy Bodies), the prevalence is higher and so it is the severity of the symptoms. [30] One potential explanation for this increased prevalence of depression in PD and APD is the loss of neurotransmitters such as dopamine, serotonin, and norepinephrine.

Some cross-sectional studies of PD less than half of those with depressive disturbances have major depression; most patients have milder forms of depression. [52] In one review of PD depression studies, the average prevalence of dysthymia, minor depression, and major depression was 22.5 %, 36.6 %, and 24.8 %, respectively. [38] There is opposing data defending that the prevalence of depression in PD patients and in healthy controls is similar. Therefore neurological changes of Parkinson’s disease may overlap in the diagnosis of the diverse mood disorders. [31]
Another study determined that PD patients with a history of depression before diagnosing PD had a more significant depression than those who had no such history. [42] The lack of knowledge regarding the underlying mechanisms of depression in PD makes the causality of PD and depressive disorders still controversial and unclear.

The aetiology of depression is different in every individual. There is great diversity of the neurobiological hypotheses about depression, some of them are: genetic vulnerability, altered HPA axis activity, deficiency of monoamines, dysfunction of specific brain regions, neurotoxic and neurotrophic processes, reduced GABAergic activity, dysregulation of glutamate system, and Lastly impaired circadian rhythms. Whether the trigger of depression is based on heterogeneous theories or a single unified hypothesis is unsure. [32]

Some investigations to proof the biological basis of the mood disorders were conducted in Cohort studies commenting on the different traits of premorbid parkinsonian personality. From the results obtained, the personality of PD patients would be described as more tense, nervous, serious, introverted, they avoid risky behaviours, they are also less impulsive, honest; and that they are less likely to exhibit novelty-seeking behaviour compared to controls. [34, 35, 36] Despite these common findings occurring in early stages of PD, the results are insufficiently specific and these traits cannot be used to predict reliably increased risk of PD in the general population.

It is well known that relatives of PD patients have an increased risk of suffering PD and other neurologic disorders; [37,38] raising evidence suggesting that depressive disorders and anxiety disorders share familial susceptibility factors with PD has been also discovered. [39]

Seeking for the reason of this genetic association, the role of parkin mutations (PARK2 on chromosome 6q, risk factor in early-onset PD) [40] was carefully studied among early-onset
PD patients affected by depression and their relatives. The study (Srivastava et al) concluded that there is enough evidence supporting a genetic contribution to depression, and relatives of early-onset PD cases with parkin mutations and without diagnosed PD may have a higher risk of depression compared to relatives without these mutations proving a possible casualty. [41]

Diagnosis of depression:

Premorbid neuropsychiatric symptoms of PD are not well recognised in clinical practice. A US study reported that existing depression, anxiety, and fatigue are not identified by neurologists in more than 40% of the patient consultations. [43]

A systematic review examined the tools for detecting depression in PD, detecting three sensitive and specific tools: the GDS-15, BDI-I/1a, and MADRS. The results of this review presented the GDS-15 as the most accurate screening tool for depression in this population given its higher sensitivity (at 91%). The availability in the public domain for being copyright free and its practicability for using only few resources make this tool the best detection resource. The GDS has also been translated into many different languages and has a collateral source version. [46]

3. Conclusions and recommendations

Summarising and investigating carefully the different NMS, their utility in the diagnosis of early PD, as well as the possibility of predicting a negative prognosis and co-morbidities (eg., dementia) these are some deductions of the most useful premotor biomarkers of the PD: the first NMS of Parkinson are mainly detected by a proper clinical evaluation of PD. These biomarkers have diverse predictive value for PD diagnosis. Many are likely to help with early diagnosis, and show high specificity or sensitivity, such as RBD, olfactory dysfunction, and dopaminergic imaging tests

the detection of hyposmia in PARS individuals will play a significant role in future investigations of the PD while it will also be a great tool for:

- Early premotor diagnosis
- Differential diagnosis
- Prognosis
- Biomarker of disease progression

Secondly, RBD must be targeted in the future clinical trials on the progression of cognitive decline in PD, and it should be clearly identified in primary health care as a risk factor for...
PD, therefore the diseased patients will be named PARS and included in future neuroprotective trials.

Concerning constipation, the keystone for the diagnosis and association with PD would be the estimation of the pathophysiology of functional constipation prior PD in order to enhance the therapeutic quality and earlier diagnosis. The etiology remains ambiguous being the hypothesis of loss of neuronal density in the myenteric ganglion and the deposition of alpha synuclein in the colon and the most recent hypothesis based on the differences in the gut’s flora. The latest one should be meticulously reassessed detecting metabolites to recognise the microbial functions that may interact with the human body during the development of PD and to determine precise hypotheses about how the microbiome may be involved in this process.

Lastly, studies of depression in PD patients can not absolutely clarify the difference of prevalence in major depression, minor depression, depressive symptoms or mood disorders. The conclusions of these investigations therefore are still diverse and controversial. As well as contradictory when they explain the prevalence in the general population and PD patients, and its causality. Due to these vague information, future research should focus on explaining the inhomogeneous uncertain findings among minor and major depression in PD. Moreover, the investigation about the diagnosis of the novel cases in PD should take into consideration the possible overlap between neurological and depressive symptoms. The clinician’s interest must not be exclusively on motor impairment (the psychiatric symptoms will be missed), more mood traits should be taken into consideration as well as the possible reluctance of the patients admitting these pathologic features.

Primary health care professionals should be updated in all the last clinical matters in order to recognise the first NMS in PARS individuals or diagnose the patients at risk, and apply the available neuroprotective therapies in time as well as include these individuals in the future trials.

The following table gathers the summary of information of the strongest NMS as biomarkers for PD that can be used in clinical practice.
<table>
<thead>
<tr>
<th>Symptoms assessed</th>
<th>Prevalence prior PD diagnosis (%PD vs %HC)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Cost of testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyposmia</td>
<td>35.5 vs 17.7 (exceeding 85% of early PD patients)</td>
<td>HIGH (87% approx. and ability to differentiate from other APD)</td>
<td>HIGH</td>
<td>LOW</td>
</tr>
<tr>
<td>RBD</td>
<td>17.9 vs X (88% using Unified Parkinson's Disease Rating Scale score &gt;4, 2 years prior PD diagnosis)</td>
<td>HIGH (RBD is considered a PARS, almost 80% of patients are at risk of suffering PD in 10 years)</td>
<td>HIGH</td>
<td>HIGH</td>
</tr>
<tr>
<td>Constipation</td>
<td>20 vs 9.3 (79% from Honolulu-Asia Aging Study [12,51])</td>
<td>MODERATE</td>
<td>LOW (20% prior 2 years of PD diagnosis, 10% in controls)</td>
<td>LOW</td>
</tr>
<tr>
<td>Depression</td>
<td>23 vs 14.9 (40% of PD patients diagnosed)</td>
<td>LOW</td>
<td>LOW (results are contradictory and controversial in the causality and type of depression or mood disorder)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

Table No. 1
References


