Non-motor symptom burden grading as predictor of cognitive impairment in Parkinson's disease

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Abstract

Background: Identify predictors of incident cognitive impairment (CI), one of the most problematic long-term outcomes, in Parkinson's disease (PD) is highly relevant for personalised medicine and prognostic counselling. The Non-Motor Symptoms Scale (NMSS) provides a global clinical assessment of a range of NMS, reflecting NMS burden (NMSB), and thus may assist in the identification of an "at-risk" CI group based on overall NMSB cut off scores.

Methods: To investigate if specific patterns of PD NMS profiles predict incident CI, we performed a retrospective longitudinal study on a convenience sample of 541 non-demented PD patients taking part in the Non-motor Longitudinal International Study (NILS) cohort, with Mini-Mental State Examination (MMSE), NMSS and Scales for Outcomes in PD Motor Scale (SCOPA Motor) scores at baseline and last follow-up (mean 3.2 years) being available.

Results: PD patients with incident CI (i.e., MMSE score ≤25) at last follow-up (n=107) had severe overall NMSB level, significantly worse NMSS hallucinations/perceptual problems and higher NMSS attention/memory scores at baseline. Patients with CI also were older and with more advanced disease, but with no differences in disease duration, dopamine replacement therapy, sex, and comorbid depression, anxiety and sleep disorders.

Conclusions: Our findings suggest that a comprehensive baseline measure of NMS and in particular hallucinations and perceptual problems, assessed with a validated single instrument can be used to predict incident CI in PD. This approach provides a simple, holistic strategy to predict future CI in this population.

Introduction

Cognitive impairment (CI) is one of the most prominent and clinically relevant non-motor features in Parkinson's disease (PD),[1] being an indicator for poor quality of life for patient as well as carers and having a significant impact on societal and institutionalisation related costs.[2] The spectrum ranges from subtle cognitive changes, through mild CI (PD-MCI) with no significant difficulties of daily living, to PD dementia (PDD) with substantially affected daily functioning and a greater degree and variety of cognitive deficits.[1] The identification of predictors of CI is highly relevant for (a) personalised management strategies (e.g., advanced counselling, avoiding anticholinergics and earlier use of cholinesterase inhibitors)[3] and (b) enriching trial populations for potential neuroprotection and palliative care.[4] Based on the available evidence, several clinical and demographic factors such as higher age at PD onset, fewer years of formal education, increasing severity of disease, and psychiatric disorders (e.g., depression and psychosis) predict future development of PDD.[5,6,7,8]

An approach to address the development of potential CI in PD, using for example a validated and widely used NMS burden (MNSB) grading system[2,9] seems intuitively reasonable, given the reported links of CI with disease severity[2,5,6] clinical subtypes[10], neuropathological burden[11] and drug treatment (NMSB grading may also reflect drug-induced NMS for instance).[12] NMSB grading provides a simple, yet comprehensive method for quantifying PD NMS load[13] and can be used as a clinical biomarker[14]. The PD Non-Motor Symptoms Scale (NMSS) remains the only scale (recently updated as MDS-NMS) as a specific measure of a range and nature of NMS and validated cut offs for NMSB have been published.[9,15]

In an effort to identify possible clinical predictors of CI in PD using one comprehensive tool we aimed to explore two issues: (a) which out of the nine NMSS domains are associated with

CI in PD patients, using a large-scale cohort and a "real life" data mining-based analysis and (b) does a higher NMSB at baseline predict to CI after 3 years. Our hypothesis was that the burden of specific NMS and total NMSB in a large cohort of PD patients could be different in those who developed CI at follow up from those who did not.

Methods

For this analysis, we selected a longitudinal dataset of 541 consecutive PD patients taking part in the Non-motor Longitudinal International Study (NILS) at King's College Hospital for whom Mini-Mental State Examination (MMSE) scores were available and who had at least one follow-up assessment as part of NILS. NILS was adopted by the National Institute of Health Research in the United Kingdom (UKCRN No. 10084) as the first comprehensive longitudinal study identifying non-motor profiles in PD, as well as the natural history of NMS, treatment response and clinic-pathological-imaging correlations. The study was authorised by local ethics committees (NRES SouthEast London REC3, 10084, 10/H0808/141). All patients gave written consent prior to study procedures in accordance with the Declaration of Helsinki and Good Clinical Practice.

Data were analysed from a cumulative cohort of PD patients recruited between November 2011 (start of NILS data collection) and July 2019 (data extracted on 1 July 2019) and only data from patients included in the United Kingdom were analysed. The main inclusion criterion was diagnosis of idiopathic PD according to the UK Brain Bank criteria. We only included data from the baseline assessments and at last follow-up in the analysis. All included patients were non-demented at baseline as defined by an MMSE score ≥ 28.[16] Exclusion criteria were (1) diagnosis of Parkinsonism different to idiopathic PD; (2) inability to give consent to participate in the study. The patient cohort was divided into two groups based on the MMSE scores at

follow-up: cognitively normal (CN) (MMSE score of ≥26) or cognitively abnormal (CA) (MMSE score of ≤25).[17]

Demographic data of the included PD patients contained information regarding age, sex, disease duration and duration of follow-up. In our analysis, we used data from Hoehn and Yahr (HY) staging,[18] Non-Motor Symptoms Scale (NMSS), levodopa equivalent dose (LEDD),[19] MMSE[20] and SCales for Outcomes in PArkinson's disease (SCOPA)-MOTOR,[21] comprising of -motor examination (SCOPA-ME, activities of daily living (SCOPA-ADL), and motor complications (SCOPA-MCompl) assessments. The NMSS facilitates a rater-administered comprehensive assessment of NMS in PD patients, and includes 30 items grouped in nine relevant domains: 1) cardiovascular including falls, 2) sleep/fatigue, 3) mood/apathy, 4) perceptual problems/hallucinations, 5) attention/memory, 6) gastrointestinal tract, 7) urinary function, 8) sexual function, and 9) miscellaneous. The NMSS Score for each item is based on a multiplication of severity (from 0 to 3) and frequency (from 1 to 4) scores.[15] Furthermore, we included data from patient-reported outcomes (i.e., Hospital Anxiety and Depression Scale (HADS-total); a 14-item, patient-completed scale with subscales for anxiety and depression[22]; PD Sleep Scale-version 1 (PDSS) and a 15-item, patient-completed clinical tool used to assess the frequency of sleep disturbances during the past week in PD patients).[23] Using overall NMSS scores the levels of NMSB were determined based on the validated cut offs of the published NMSB grading system.[9] NMSS total score of 0 is related to "no", 1-20 to "mild", 21-40 to "moderate", 41-70 to "severe" and ≥71 to "very severe" NMSB level.[9]

Data are represented as mean and standard deviation, median [interquartile range], or number (percentage), unless otherwise specified. Group differences were tested using the Mann-Whitney test and intragroup differences (baseline to follow-up) were tested using the Wilcoxon

signed rank test, as the data used in this study were not normally distributed ($p \leq 0.001$; Shapiro-Wilk test). The significance threshold was set at 0.05. A Quade's rank analysis of covariance was performed to correct for statistically significant differences in age between the two groups at baseline and a Benjamini-Hochberg correction was used in case of multiple comparisons. To test for differences of gender and NMSB levels Pearson Chi-square analysis was used. To estimate the association between the score of baseline clinical evaluations and the incident CI at follow up, two binary logistic regression models were performed, using the dichotomized MMSE at follow-up defined as normal (≥26) and abnormal (<26) as dependent variable. The independent variables in the first model were LEDD, PD duration, PDSS, SCOPA Motor and NMSS total scores at baseline. In the second model the NMSS domains scores at baseline replaced NMSS total scores. The rest of variables were not included due to possible collinearity. Both regression models were adjusted for age and gender. All data were analysed using SPSS Version 25 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

Results

Of the 541 patients of our study, 434 had normal cognitive function at follow-up (CN group) and 107 had CI (CA group). Mean duration of follow-up was 3.18±1.48 years (minimum 0.6, maximum 6.9 years) for the CN and 3.28±1.79 years (minimum 0.4 years, maximum 7.2 years) for the CA group. At baseline the 434 patients in the CN group had mean age 64.44±11.27 years, disease duration 5.43±5.21 years, median HY stage 2 [1.0-3.0] and NMSS total score 45.19±35.29. 24.1% (n=104) of these patients had mild, 30.8% (n=133) moderate, 24.1% (n=104) severe and 19.9% (n=86) very severe NMSB level at baseline. Patients in CA group (n=107) had a mean age of 70.66±8.64, disease duration of 5.63±5.36) years, median HY stage 2 [2.0-3.0] and NMSS total score 52.76±40.97 at baseline. 24.3% (n=26) of these

patients had mild, 24.3% (n=26) moderate, 19.6% (n=21) severe and 30.8% (n=33) very severe NMSB level at baseline. The two groups were well matched regarding gender (p=0.15), duration of disease (p=0.79), follow-up (p=0.74), and LEDD (p=0.66). Furthermore, as per inclusion criteria all patients were non-demented at baseline, as defined by MMSE of ≥28. Importantly no statistical differences were found in total NMSS scores between groups at baseline (p=0.41), nor in distribution of NMSB grading (p=0.15). Nonetheless, patients from the CA group were significantly older (p< 0.001) and showed, moreover, significantly higher scores in SCOPA-ME (p= 0.004), SCOPA-ADL (p= 0.004) compared with the CN patients at baseline. (**Table 1**)

In terms of the NMSS domain scores at baseline, the patients of the CA group had significantly higher scores in domain 4 (perceptual problems/hallucinations) (p=0.024) compared with the CN patients. No significant differences between the two groups of patients were found at baseline in domains 1 (cardiovascular), 2 (sleep/fatigue), 3 (mood/apathy), 6 (gastrointestinal tract), 7 (urinary function), 8 (sexual function) and 9 (miscellaneous) of NMSS (p≥0.48) or in HADS-total, SCOPA-MCompl and PDSS scores (p≥0.45). No significant differences were also found in NMSS domain 5 (attention/memory) (p=0.2) and HY stage (p=0.06) despite the trend towards statistical significance founded in the analysis without correction for age and multiple testing. **(Figure 1)**

At follow up, patients in the CA group showed significantly higher median HY scores (3.0 [2.0-3.0] vs. 2.5 [2.0-3.0]: p=0.019), NMSS total scores (60.72±43.11 vs. 46.26±37.90: p= 0.003), NMS cardiovascular domain scores (2.27±3.60 vs. 1.61±2.68: p= 0.033), sleep/fatigue domain scores (11.17±9.08 vs. 9.40±9.02: p= 0.033), mood/apathy domain scores (10.12±12.43 vs. 7.23±11.85: p= 0.010), perceptual problems/hallucinations domain scores

(3.44±5.02 vs. 1.77±3.72: p = 0.003), attention/memory domain 5 scores (8.81±8.45 vs. 4.79±6.79: p< 0.001), as well as of SCOPA-ME scores (13.65±5.55 vs. 10.35±5.11: p< 0.001), SCOPA-ADL scores (8.93±3.80, vs. 6.46±3.82: p< 0.001), HADS-total scores (13.97±7.69 vs. 11.29±6.81: p= 0.003) compared to CN patients. No significant differences were observed in any of the other used clinical assessments. **(Figure 2)**

In order to identify the important baseline predictive factors of relevant CI at follow-up we designed two binary regression models. In the first regression model, retained variables were age (odds ratio, OR: 1.06; 95% confidential interval, 95% CI: 1.03-1.08) and SCOPA-ME (OR: 1.07; 95% CI: 1.02-1.11) at baseline. In the second model, NMSS domain 4 (perceptual problems/hallucinations) scores at baseline were retained (OR: 1.10; 95% CI: 1.02-1.19) together with age (OR: 1.05; 95% CI: 1.03-1.08) and SCOPA-ME (OR: 1.06; 95% CI: 1.01-1,10) at baseline. **(Table 2)**

Discussion

In this large scale, longitudinal cohort based retrospective analysis we showed that:

1. PD patients who developed CI over the 3.2 years follow up period had significantly worse NMSS baseline scores for hallucinations/perceptual problems with no baseline intergroup differences in disease duration, dopaminergic medication, gender and presence of depression, anxiety and sleep disorders.
2. Higher burden of hallucinations/perceptual problems, but not overall non-motor burden at baseline, predicted CI in PD, which suggests that these symptoms are likely to precede CI, as measured by objective screening tools such as the MMSE.

We believe that this may be the first study which examined whether CI could be predicted using a single instrument such as the NMSS. CI in PD is, similar to other PD symptoms,

heterogeneous and usually occurs concomitant with a variety of other NMS and associated burden of NMS.[2] Thus, a comprehensive method for quantifying PD manifestations such as CI in the context of other NMS is worthwhile, especially in prodromal stages.[13] The NMSS encompasses practically and quantitatively the severity and frequency of NMS of patients with PD including items addressing functions related to cortex and limbic system. Also validated cut offs for NMS burden have been published.[15] We did not find significant differences in distribution of overall NMSB grading between the study groups but in specific NMS domains, which was confirmed in the logistic regression models. This is in line with the concept of several NMS dominant subtypes of PD, among which the limbic and cortical subtypes both encompass aspects of cognitive deficits.[24, 25, 26] The cognitive aspect of non-motor endophenotype in PD is also supported by prodromal studies, which suggest cognitive deficit in a subset[27] and also gut based cholinergic imaging studies.[28]

Our results regarding significant higher baseline NMSS scores for hallucinations and perceptual problems (as reflected by the total scores for Doman 4 of the NMSS) are consistent with previous studies, which have shown that psychotic symptoms in PD, including delusions and hallucinations, are risk factors for the development of dementia and predictors of poor prognosis, mortality, and nursing home placement.[7, 29] The two groups in our study did not differ in disease duration and LED, so the difference in NMSS hallucinations/perceptual problems scores is unlikely to be the result of duration and dopaminergic medication dose. Indeed, studies from the pre-levodopa era did mention hallucinations as part of disease manifestations.[30] Besides, contrary to the results of other studies, in which sleep disorders were identified to be predictors of CI[31]; we did not find any differences in overall PDSS scores between CA and CN groups at baseline. Moreover, we found that the patients in the CA group were significantly older, showed significantly higher SCOPA-ME and -ADL scores and had a

trend towards significantly more advanced HY stage compared with the patients in the CN group at baseline. These results are in line with previous studies, which provide clear evidence that age, motor impairment and measures of impairment in daily activities at baseline disease could predict the CI of patients.[32] Using Quade's rank analysis of covariance correction we could show that the observed statistically significant higher NMSS domain 4 score in the patients of CA group was not due to age difference in the group, which suggest that hallucinations/perceptual problems might be initial manifestation of a subgroup of PD patients predisposed to CI and higher motor scores and age seem to be independent predictors, as also identified in our regression analyses.

Our analysis also revealed a trend towards significantly higher scores in the NMSS domain 5 (attention/memory) in the CA group compared to CN group at baseline. A 2-step meta-analysis comparing 30 neuropsychological tests of multiple cognitive domains showed that in non-demented PD patients memory, additionally to the more commonly reported domains of attention and executive function are impaired.[33] This study is consistent with ours, as cognitive domains of memory and attention are addressed by the question in domain 5 of NMSS. In terms of other neuropsychiatric symptoms such as depression and anxiety measured by HADS at baseline, our analysis did not reveal any significant differences. These findings are not consistent with other studies indicating that depression and anxiety are predictors of CI in PD.[34] Moreover, male sex has been proposed to be associated with CI as opposed to findings of our study, were no gender differences were found.[35] Our results suggest that the development of clinically relevant CI, appears to be preceded by patient-reported attention and memory problems before these can be objectified using formal cognitive assessment screening tools, such as the MMSE, but this phenomenon is not independent from age, gender and the other baseline clinical characteristics of our cohorts.

A link between psychotic symptoms, attention/memory problem and development of CI in non-demented PD patients has been reported.[29] Cholinergic dysfunction appears to be a common pathophysiological mechanism and cholinergic endophenotype of PD has been proposed.[1,36,37] Neuropathological studies from PD patients with visual hallucinations showed atrophy in the pedunculopontine nucleus and nucleus basalis of Meyner,[38,39] which suggest the involvement of cholinergic system in the pathogenesis of hallucinations in PD. Moreover, in PD patients without a CI, such as the cohort of our study at baseline, lower cortical acetylcholinesterase positron-emissions-tomography activity was associated with reduced cognitive performance scores for attention, memory and executive functions. [1] Our results may thus indicate that higher burden of hallucinations/ perceptual and attention/memory problems might be a marker for the "cholinergic endophenotype" of PD which has therapeutic connotations.[40] In clinical practice, our findings suggest that, in patients with concomitant higher burden of perceptual and attention/memory problems, corresponding higher score in NMSS domain 4 and 5, the awareness of dementia development also in the next 3 years should be considered in relation to advanced planning and directive. Therefore, screening of PD patients with NMSS in addition to MMSE might be a useful method of predicting CI. This could have major potential clinical impact in relation to personalised medicine, enriching cohorts for neuroprotective studies, advanced directives as well as focussed palliative care and caregiver support.

The retrospective design and a relatively short and variable follow-up are the main limitations of this study, which should be addressed in future studies. For the diagnosis of idiopathic PD the UK PD Brain Bank criteria were applied, because the start of data collection for our cohort dates back 2011, where the revised Movement disorder society (MDS) PD criteria[41] were not available, and even now, some of the requisites for the 2015 MDS PD criteria such as objective testing of olfaction, cardiac metaiodobenzylguanidine (MIBG) scans are

not routinely performed at diagnosis. In addition, we used only MMSE as an instrument to evaluate the CI in PD. This was because at the time of the setup of NILS in 2010 MMSE was recommended as the tool for cognitive assessment by the steering group of NILS. Despite its debatable accuracy and sensitivity, especially in mild cognitive deficits in PD patients, MMSE is still recommended as the primary screening instrument for PDD[42] and used as a longitudinal test.[43] We used the threshold of 25 score of MMSE at endpoint follow up to dichotomise our cohorts and form the CA and CN groups. Scores under 25 are widely used to define the start of CI, relevant in daily life and therefore fulfilled the main criterion of dementia, as recommended from the movement disorder society task for PDD.[17] At baseline the MMSE score between the groups was also significant different, but not relevant in clinical practice as the difference was only 0.66 (mean) and MMSE score was above 28 as per inclusion criteria. The NMSS is a validated tool for assessing NMS in PD patients, reflecting a real-world experience; however, NMSS contains only three items addressing cognitive domains, which are mainly assessed by history taking and are not an objective cognitive test. The strength of our study was that we studied a large number of patients (n=541) and a diversity of variables regarding demographics and outcome of PD patients and we corrected for age and multiple comparisons.

To conclude, our results suggest that non-motor profiling of PD patients by using the NMSS could be useful in aiding the prediction of CI development in PD patients over an average period of three years. Moreover, it can contribute to categorising patients into a subgroup, where cholinergic systems might be pathophysiologically involved. High scores on the hallucinations/psychosis domain of the NMSS should alert the clinician to the likelihood that PD patients would develop CI over the coming years, preceding changes in more objective

cognitive screening tools, such as the MMSE. In addition to sophisticated and detailed tools to predict CI, the NMSS system adds a pragmatic, quick win based strategy that can be widely applicable even in non-specialised clinics.

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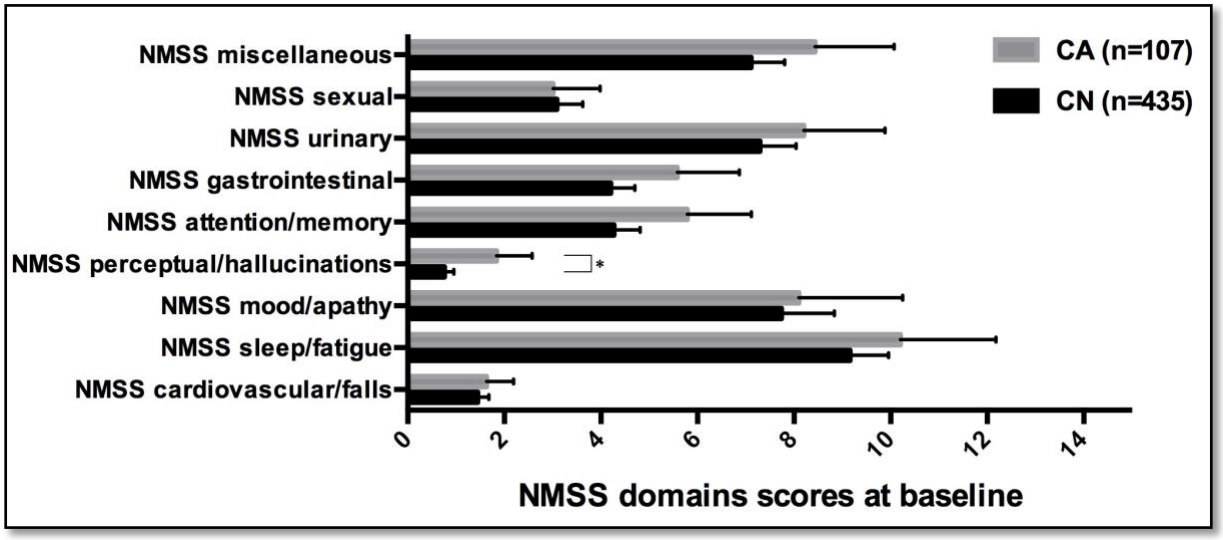
The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Table 1: Descriptive statistics of the study groups at baseline and at follow up. Data are represented as mean ± standard deviation, unless otherwise specified. Group differences tested using Mann-Whitney U test.

	Baseline					
Baseline demographics	**CA (n=107)**	**CN (n=435)**	**P [1]**	**P [2]**	**CA (n=107)**	
Age (ys)	70.66±8.64	64.44±11.27	**<0.001**	N/A	73.78±8.46	
Gender (M/F)	69.2%/30.8%	61.8%/38.2%	0.159	0.318	69.2%/30.8%	
Disease duration (ys)	5.63±5.36	5.43±5.21	0.798	0.798	8.81±5.85	
Duration follow-up (ys)	3.18±1.48	3.28±1.79	0.743	0.798	N/A	
LEDD (mg)	473.37±407.35	512.70±475.03	0.667	0.798	728.02±460.96	6
HY †	2.0 [2.0-3.0]	2.0 [1.0-3.0]	**0.023**	0.061	3.0 [2.0-3.0]	
Outcome measures						
SCOPA-ME	11.36±5.36	9.40±4.89	**0.001**	**0.004**	13.65±5.55	
SCOPA-ADL	6.23±3.45	4.98±3.29	**0.001**	**0.004**	8.93±3.80	
SCOPA-MCompl	1.68±2.82	1.61±2.52	0.592	0.798	1.98±2.12	
NMSS cardiovascular/falls	1.63±2.91	1.45±2.47	0.642	0.963	2.27±3.60	
NMSS sleep/fatigue	10.20±10.32	9.16±8.45	0.771	0.973	11.17±9.08	
NMSS mood/apathy	8.10±11.21	7.74±11.63	0.892	0.973	10.12±12.43	
NMSS perceptual/hallucinations	1.84±3.82	0.76±2.05	**0.002**	**0.024**	3.44±5.02	
NMSS attention/memory	5.79±6.90	4.27±5.80	**0.034**	0.204	8.81±8.45	
NMSS gastrointestinal	5.58±6.71	4.20±5.35	0.071	0.284	6.06±6.23	
NMSS urinary	8.20±8.77	7.29±8.00	0.322	0.552	8.56±9.29	
NMSS sexual	3.01±5.06	3.09±5.66	0.892	0.973	1.88±4.70	
NMSS miscellaneous	8.43±8.57	7.11±7.42	0.223	0.454	8.60±8.50	
NMSS total	52.76±40.97	45.19±35.29	0.139	0.417	60.72±43.11	
PDSS total	109.92±27.48	107.36±25.51	0.227	0.454	95.23±29.07	
HADS total	11.01±7.44	10.77±6.47	0.985	0.985	13.97±7.69	

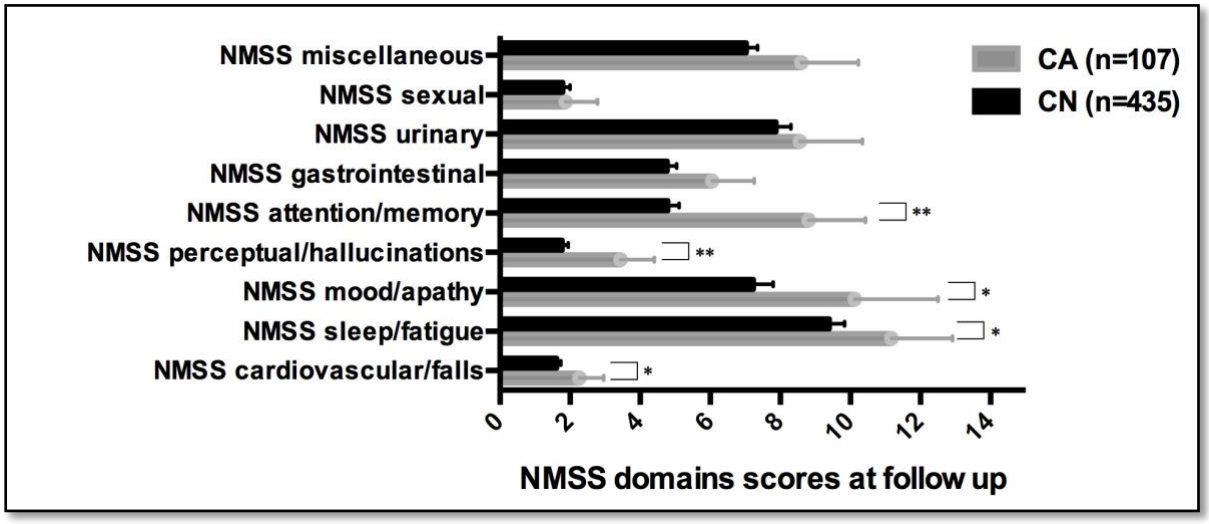
CA, cognitively abnormal (MMSE score of ≤25 at follow up); CN, Cognitively normal (MMSE score of ≥26 at follow up); N, number; [1], Uncorrected p-values; [2], P-values corrected for age (Quade's rank analysis of covariance correction) and multiple testing (Benjamini-Hochberg procedure); †, Median [25th-75th percentile]. Ys, years; M, male; F, female; HY, Hoehn and Yahr; LED, Levodopa equivalent dose; SCOPA, SCales for Outcomes in PArkinson's disease; -ME, motor examination; -ADL, - activities of daily living; - MCompl, motor complications; NMSS, non-motor symptom scale; HADS, hospital anxiety and depression scale; PDSS, Parkinson's disease sleep scale.

Figure 1: NMSS domains scores between the study groups at baseline. Data presented as mean and 95% confidence intervals (bars).



CA, cognitively abnormal (MMSE score of ≤25 at follow up); CN, Cognitively normal (MMSE score of ≥26 at follow up). * Indicates a p value of 0.024 (Quade's rank analysis of covariance correction for age and Benjamini-Hochberg procedure correction for multiple testing); The NMSS Score for each item is based on a multiple of severity (from 0 to 3) and frequency (from 1 to 4) scores.

Figure 2: NMSS domains scores between the study groups at follow up. Data presented as mean and 95% confidence intervals (bars).



CA, cognitively abnormal (MMSE score of ≤25 at follow up); CN, Cognitively normal (MMSE score of ≥26 at follow up). * Indicates a p value <0.05 (Quade's rank analysis of covariance correction for age and Benjamini-Hochberg procedure correction for multiple testing); ** indicates a p value <0.005 (Quade's rank analysis of covariance correction for age and Benjamini-Hochberg procedure correction for multiple testing); The NMSS Score for each item is based on a multiple of severity (from 0 to 3) and frequency (from 1 to 4) scores.

Table 2: Results of logistic regression models. First model: Dependent variable; the dichotomized MMSE at follow-up defined as MMSE_FU_REC: 0=normal (≥26); 1=abnormal (<26). Independent variables were Levodopa equivalent dose (LED), PD duration, Parkinson's disease sleep scale (PDSS), SCales for Outcomes in PArkinson's disease -motor examination (SCOPA-ME) and non-motor symptom scale (NMSS) total scores at baseline. Second model: Dependent variable; defined as MMSE_FU_REC: 0=normal (≥26); 1=abnormal (<26). Independent variables LED, PD duration, PDSS, SCOPA-ME and NMSS domains scores at baseline. Only data for significant predictors are shown.

	B	p-value	OR	95% C.I.for OR	
				Lower	Upper
First Model					
Age	0.055	<0.001	1.057	1.033	1.081
SCOPA-ME	0.067	0.002	1.069	1.025	1.116
Constant	-5.828	<0.001	0.003		
Second Model					
Age	0.053	<0.001	1.055	1.031	1.079
SCOPA-ME	0.054	0.017	1.056	1.010	1.103
NMSS domain 4	0.097	0.014	1.102	1.020	1.191
Constant	-5.681	<0.001	0.003		

B, Beta value; OR: Odds Ratio. C.I., confidence interval; NMSS domain 4, perceptual problems/hallucinations

References

1. Aarsland D, Creese B, Politis M, et al. Cognitive decline in Parkinson disease. Nat Rev Neurol 2017;13(4):217–231.

2. Goldman, J.G., Vernaleo, B.A., Camicioli, R. et al. Cognitive impairment in Parkinson’s disease: a report from a multidisciplinary symposium on unmet needs and future directions to maintain cognitive health. npj Parkinson's Disease 2018;4:19.

3. Titova N, Chaudhuri KR. Personalized medicine in Parkinson's disease: Time to be precise. Mov Disord 2017;32(8):1147–1154.

4. Pablo Martinez-Martin & Kallol Ray Chaudhuri. Comprehensive grading of Parkinson’s disease using motor and non-motor assessments: addressing a key unmet need, Expert Review of Neurotherapeutics 2018; 18(1): 41-50.

5. Liu G, Locascio JJ, Corvol JC, et al. Prediction of cognition in Parkinson's disease with a clinical-genetic score: a longitudinal analysis of nine cohorts. Lancet Neurol 2017;16(8):620–629.

6. Anang JB, Gagnon JF, Bertrand JA, et al. Predictors of dementia in Parkinson disease: a prospective cohort study. Neurology 2014;83(14):1253–1260.

7. Szatmari S, Illigens BM, Siepmann T, Pinter A, Takats A, Bereczki D. Neuropsychiatric symptoms in untreated Parkinson's disease. Neuropsychiatr Dis Treat. 2017;13:815–826.

8. Marinus J, Zhu K, Marras C, Aarsland D, van Hilten JJ. Risk factors for non-motor symptoms in Parkinson's disease. Lancet Neurol 2018; 17(6):559-568.

9. Ray Chaudhuri K, Rojo JM, Schapira AH, et al. A proposal for a comprehensive grading of Parkinson's disease severity combining motor and non-motor assessments: meeting an unmet need. PLoS One 2013;8(2):e57221.

10. Marras, C. and Chaudhuri, K.R. Nonmotor features of Parkinson's disease subtypes. Mov Disord 2016;31(8):1095-102.

11. Halliday, G. M., Leverenz, J. B., Schneider, J. S. & Adler, C. H. The neurobiological basis of cognitive impairment in Parkinson’s disease. Mov. Disord 2014; 29 (5): 634–650.

12. Goldman, J.G. and Weintraub, D. Advances in the treatment of cognitive impairment in Parkinson's disease. Mov Disord 2015; 30(11): 1471-1489.

13. Martinez-Martin, P. Instruments for holistic assessment of Parkinson’s disease. J Neural Transm 2013; 120(4):559-64.

14. Pablo Martinez-Martin & Kallol Ray Chaudhuri. Comprehensive grading of Parkinson’s disease using motor and non-motor assessments: addressing a key unmet need. Expert Review of Neurotherapeutics 2018; 18 (1): 41-50.

15. Chaudhuri KR, Martinez-Martin P, Brown RG, Sethi K, Stocchi F, Odin P, Ondo W, Abe K, Macphee G, Macmahon D, Barone P, Rabey M, Forbes A, Breen K, Tluk S, Naidu Y, Olanow W, Williams AJ, Thomas S, Rye D, Tsuboi Y, Hand A, Schapira AH. The metric properties of a novel non-motor symptoms scale for Parkinson’s disease: results from an international pilot study. Mov Disord 2007;22(13):1901-11

16. O'Bryant SE, Humphreys JD, Smith GE, et al. Detecting dementia with the mini-mental state examination in highly educated individuals. Arch Neurol 2008;65(7):963–967.

17. Dubois, B., Burn, D., Goetz, C., Aarsland, D., Brown, R.G., Broe, G.A., Dickson, D., Duyckaerts, C., Cummings, J., Gauthier, S., Korczyn, A., Lees, A., Levy, R., Litvan, I., Mizuno, Y., McKeith, I.G., Olanow, C.W., Poewe, W., Sampaio, C., Tolosa, E. and Emre, M. Diagnostic procedures for Parkinson's disease dementia: Recommendations from the movement disorder society task force. Mov. Disord 2007;22(16):2314-24.

18. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17(5):427–442.

19. Tomlinson, C.L., Stowe, R., Patel, S., Rick, C., Gray, R. and Clarke, C.E. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov. Disord 2010;25(15):2649-53.

20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research 1975;12(3):189-98.

21. Marinus J, Visser M, Stiggelbout AM, Rabey JM, Martínez-Martín P, Bonuccelli U, Kraus PH, van Hilten JJ. A short scale for the assessment of motor impairments and disabilities in Parkinson's disease: the SPES/SCOPA. J Neurol Neurosurg Psychiatry 2004;75(3):388-395.

22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67(6):361-70

23. Chaudhuri KR, Pal S, DiMarco A, Whately-Smith C, Bridgman K, Mathew R, Pezzela FR, Forbes A, Högl B, Trenkwalder C. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. J Neurol Neurosurg Psychiatry 2002;73(6):629–635.

24. Sauerbier A, Jenner P, Todorova A, Chaudhuri KR. Non motor subtypes and Parkinson's disease. Parkinsonism Relat Disord 2016;22(1):41-46.

25. Zis, P., Martinez Martin, P., Sauerbier, A., Rizos, A., Sharma, J.C., Worth, P.F., Sophia, R., Silverdale, M. and Chaudhuri, K.R. Non-motor symptoms burden in treated and untreated early Parkinson's disease patients: argument for non-motor subtypes. Eur J Neurol 2015;22(8):1145-50.

26. Van Rooden SM, Heiser WJ, Kok JN, Verbaan D, van Hilten JJ, Marinus J. The identification of Parkinson's disease subtypes using cluster analysis: a systematic review. Mov Disord 2010; 25(8):969-78.

27. Weintraub D, Simuni T, Caspell-Garcia C, et al. Cognitive performance and neuropsychiatric symptoms in early, untreated Parkinson's disease. Mov Disord 2015;30(7):919–927.

28. Knudsen K, Fedorova TD, Hansen AK, et al. In-vivo staging of pathology in REM sleep behaviour disorder: a multimodality imaging case-control study. Lancet Neurol 2018;17(7):618-628

29. Ffytche DH, Creese B, Politis M, et al. The psychosis spectrum in Parkinson disease. Nat Rev Neurol 2017;13(2):81-95.

30. Fenelon G, Goetz CG, Karenberg A. Hallucinations in Parkinson disease in the prelevodopa era. Neurology. 2006;66(1):93–98.

31. Onofrj, M., Thomas, A., D'Andreamatteo, G. et al. Incidence of RBD and Hallucination in Patients Affected by Parkinson's Disease: 8-year Follow-Up. Neurol Sci 2002;23(Suppl 2): s91.

32. Zhu K, van Hilten JJ, Marinus J. Predictors of dementia in Parkinson's disease; findings from a 5-year prospective study using the SCOPA-COG. Parkinsonism Relat Disord. 2014;20(9):980–5.

33. Hoogland J, van Wanrooij LL, Boel JA, et al. Detecting Mild Cognitive Deficits in Parkinson's Disease: Comparison of Neuropsychological Tests. Mov Disord 2018;33(11):1750–1759.

34. De la Riva P, Smith K, Xie SX, Weintraub D. Course of psychiatric symptoms and global cognition in early Parkinson disease. Neurology 2014;83(12):1096–1103.

35. Cammisuli DM, Cammisuli SM, Fusi J, Franzoni F, Pruneti C. Parkinson's Disease-Mild Cognitive Impairment (PD-MCI): A Useful Summary of Update Knowledge. Front Aging Neurosci 2019;11:303.

36. Bohnen NI, Albin RL. The cholinergic system and Parkinson disease. Behav Brain Res 2011;221(2):564–573.

37. Müller ML, Bohnen NI. Cholinergic dysfunction in Parkinson's disease. Curr Neurol Neurosci Rep 2013;13(9):377.

38. Janzen J, van 't Ent D, Lemstra AW, Berendse HW, Barkhof F, Foncke EM. The pedunculopontine nucleus is related to visual hallucinations in Parkinson's disease: preliminary results of a voxel-based morphometry study. J Neurol 2012;259(1):147-154.

39. Shin S, Lee JE, Hong JY, Sunwoo MK, Sohn YH, Lee PH. Neuroanatomical substrates of visual hallucinations in patients with non-demented Parkinson's disease. J Neurol Neurosurg Psychiatry 2012;83(12):1155-1161.

40. Marras C, Chaudhuri KR, Titova N, Mestre TA. Therapy of Parkinson's Disease Subtypes [published online ahead of print, 2020 Aug 4]. Neurotherapeutics 2020;10.1007/s13311-020-00894-7.

41. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel, W, Obeso, J, Marek, K, Litvan, I, Lang, AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl, G. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015; 30:1591-1601.

42. Hoops S, Nazem S, Siderowf AD, et al. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. Neurology 2009;73(21):1738–1745.

43. Biundo R, Weis L, Antonini A. Cognitive decline in Parkinson's disease: the complex picture. NPJ Parkinsons Dis 2016;2:16018.