Journal of the Neurological Sciences 404 (2019) 124–127

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Clinical short communication

Burden of non-motor symptoms in unclear parkinsonism and tremor: A study with [^{123}I]FP-CIT SPECT

Elina Jaakkola[a,b,*], Juho Joutsa[a,b,c], Elina Mäkinen[a,b], Tommi Noponen[d,e], Miia Pitkonen[f], Reeta Levo[g], Tuomas Mertsalmi[g], Filip Scheperjans[g], Valtteri Kaasinen[a,b]

[a] Division of Clinical Neurosciences, Turku University Hospital, Turku, Finland
[b] Department of Neurology, University of Turku, Turku, Finland
[c] Turku Brain and Mind Center, University of Turku, Turku, Finland
[d] Department of Nuclear Medicine, Turku University Hospital, Turku, Finland
[e] Department of Medical Physics, Turku University Hospital, Turku, Finland
[f] Department of Nuclear Medicine, Helsinki University Hospital, Helsinki, Finland
[g] Department of Neurology, Helsinki University Hospital and Department of Clinical Neurosciences (Neurology), University of Helsinki, Helsinki, Finland

ARTICLE INFO

Keywords:
Parkinson's disease
Parkinsonism
Non-motor
Dopamine transporter
SPECT

ABSTRACT

Background: Non-motor symptoms (NMSs) are clearly more prevalent in Parkinson's disease (PD) patients compared to healthy individuals. However, NMSs are also common in the elderly and other neurological conditions, and thus, it is not known whether NMSs could be used to differentiate PD from parkinsonism/tremor without dopamine deficiency.

Methods: We prospectively evaluated NMSs immediately before brain dopamine transporter (DAT) [^{123}I]FP-CIT SPECT scanning in 193 patients with unclear parkinsonism/tremor. According to the clinical follow-up and imaging results, 84 patients had PD. NMSs and their correlations with striatal DAT binding were investigated in PD patients and in parkinsonism/tremor patients with normal dopamine function.

Results: Total NMS burden, anxiety or depression did not differ between PD patients and patients with normal DAT binding. DAT-normal patients reported more perception-related ($p = 0.045$) and attention/memory-related NMSs than PD patients ($p < 0.001$). Total NMS score did not correlate with striatal DAT binding in either group.

Conclusions: In clinically uncertain cases, the total NMS burden cannot be used as a tool in distinguishing PD patients from patients with non-dopaminergic parkinsonism/tremor. Clinical screening of NMSs appears equally important in all patients with parkinsonism.

1. Introduction

Patients with Parkinson's disease (PD) frequently sustain a multitude of non-motor symptoms (NMSs), such as depression, hyposmia and constipation, together with the classical motor symptoms [1]. NMSs may affect the quality of life of PD patients even more than motor symptoms [2]. Although there is a general consensus that NMSs are prevalent in PD and some occur even at premotor stages, the specificity of NMSs for PD is less clear. For example, NMSs are very common symptoms among elderly individuals and patients with essential tremor (ET) [3,4]. There is some evidence that dopaminergic pathophysiology may underlie, at least partly, the majority of NMSs in PD [5]. However, NMSs seem to also be common in subjects with scans without evidence of dopaminergic deficits (SWEDDs), which underlines the complexity of the issue [6].

To investigate the specificity and diagnostic value of NMSs in a clinical setting, we examined NMSs in patients undergoing [^{123}I]FP-CIT single photon emission computed tomography (SPECT). We compared NMSs in PD patients to those in patients with tremor or parkinsonism but who have normal dopamine function.

2. Methods

2.1. Patients

Patients scanned using [^{123}I]FP-CIT SPECT for clinically uncertain parkinsonism/tremor in Turku University Hospital or Helsinki University Hospital, Finland, during the years 2014–2017 were

* Corresponding author at: Division of Clinical Neurosciences, University of Turku and Turku University Hospital, POB 52, FIN-20521 Turku, Finland.
E-mail address: elanja@utu.fi (E. Jaakkola).

https://doi.org/10.1016/j.jns.2019.07.025
Received 3 April 2019; Received in revised form 20 June 2019; Accepted 18 July 2019
Available online 19 July 2019

Table 1
Main demographic and clinical characteristics and non-motor symptom scores in PD patients and in patients with normal DAT binding. Values are means (SD) [range] or n.

	PD (n = 84)	Normal DAT (n = 109)	P[a]	P[b]
Demographics				
Age (years)	65.3 (9.4) [41–82]	64.1 (12.1) [17–83]	0.875	–
Sex (male/female)	38/46	57/52	0.331	–
Motor symptom duration (months)	30.4 (44.6) [2–360]	53.0 (68.7) [3–360]	0.004	–
MDS-UPDRS motor score	38.4 (16.1) [10–73]	35.4 (16.1) [5–89]	0.205	–
H&Y	2.0 (0.9) [1–4]	2.1 (0.8) [0–5]	0.064	–
Non-motor symptoms				
MMSE	27.1 (2.4) [19–30]	26.6 (2.3) [19–30]	0.052	0.260
Depression (BDI score)	8.4 (7.7) [0–44]	10.1 (9.1) [0–42]	0.276	1.0
Anxiety (BAI score)	11.1 (6.6) [2 – 33]	14.3 (9.3) [1–50]	0.042	0.210
RBD (yes/no)	23/57	30/74	0.989	1.0
NMSS total score	55.5 (46.1) [0 – 221]	71.4 (53.4) [5–222]	0.049	0.245
Cardiovascular	1.8 (3.3) [0 – 12]	3.2 (4.1) [0–15]	0.013	0.117
Sleep/fatique	12.2 (9.9) [0–36]	12.5 (10.1) [0–45]	0.861	1.0
Mood/cognition	11.7 (17.5) [0–72]	16.9 (21.5) [0–72]	0.081	0.729
Perception	0.35 (1.6) [0–12]	0.97 (2.4) [0–12]	0.005	0.045
Attention/memory	4.4 (6.5) [0 – 33]	10.1 (11.0) [0–36]	< 0.001	< 0.001
Gastrointestinal	3.5 (4.7) [0 – 21]	4.3 (6.7) [0 – 30]	0.592	1.0
Urinary	9.5 (10.3) [0–36]	8.9 (8.2) [0–36]	0.699	1.0
Sexual	3.3 (5.9) [0–24]	4.8 (6.8) [0–24]	0.091	0.819
Miscellaneous	8.3 (7.7) [0–28]	9.6 (10.3) [0–44]	0.815	1.0

PD = Parkinson's disease, MDS-UPDRS = the Movement Disorder Society Unified Parkinson's Disease Rating Scale, H&Y = Hoehn and Yahr scale, MMSE = Mini-Mental State Examination, BDI = Beck Depression Inventory, BAI = Beck Anxiety Inventory, RBD = REM sleep behaviour disorder, NMSS = Non-Motor Symptoms Scale.

[a] T- test or Mann-Whitney U test as appropriate or Chi-Square for categorical variables.

[b] Bonferroni-correction for 5 (MMSE, BDI, BAI, RBD, NMSS total score) or 9 (NMSS subscores) comparisons.

investigated (NMDAT study; ClinicalTrials.gov identifier: NCT02650843) clinically 2–4 h before the scanning. The investigations included a clinical interview, the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III, Mini-Mental State Examination (MMSE), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), a single-question screen for REM sleep behaviour disorder (RBD) and the Non-Motor Symptoms Scale (NMSS). All investigators had completed the MDS-UPDRS Training Program and Exercise. Patients with an MMSE score < 18 were excluded from the study.

The study was accepted by the local ethics committee and was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all patients.

2.2. Scanning and image analysis

For the scanning methodology, see the Supplementary material.

2.3. Statistical analyses

IBM SPSS Statistics (version 24, SPSS Inc., Chicago, Illinois, USA) was used for statistical analyses. The differences between the two groups were calculated using either independent samples *t*-test, Mann-Whitney *U* test or Chi-square test as appropriate. Bonferroni corrections were applied for NMS total scores and separately for NMSS subscores. Analyses were performed separately in patients without anti-parkinsonian medication. Spearman correlations were used in examining the correlations between specific binding ratios (SBRs) and other variables and the correlation between symptom duration and NMSS total score. In addition, partial correlations were performed when controlling for age, MDS-UPDRS motor score and MMSE score. Log-transformations for variables with skewed distribution were performed when applicable. Voxel-wise statistical analysis methods are described in the Supplementary material.

3. Results

Out of patients with abnormal imaging outcome, only those with PD as the final clinical diagnosis were included in this study (n = 84). Patients with normal dopamine transporter (DAT) (n = 109) received the following diagnoses after SPECT scanning: clinically uncertain parkinsonian syndrome (CUPS) (n = 29), undetermined tremor (n = 21), ET (n = 18), drug-induced parkinsonism (n = 8), memory disorder or Alzheimer's disease (n = 8), vascular parkinsonism (n = 6), dystonia (n = 3), psychogenic parkinsonism (n = 3), other (n = 7) or not available (n = 6).

PD patients and DAT-normal patients did not differ in age, sex or total motor symptom severity (Table 1). There were no significant differences in total NMSS, BDI, BAI or RBD scores between PD patients and DAT-normal patients (Table 1, Fig. 1A). Additionally, there were no differences in the prevalence of depression or anxiety between the two groups when cut-off scores for BDI and BAI were used ($p > 0.10$). PD patients scored lower in NMSS perception (corrected $p = 0.045$) and NMSS attention/memory (corrected $p < 0.001$) subscales than the DAT-normal group (Table 1). Odds ratio (95% C.I.) for having PD was 0.994 (0.988–1.000) for every point increase in total NMSS score. Motor symptom duration was longer in DAT-normal patients than in PD patients ($p = 0.004$), although it did not correlate with NMSS total score in either group ($p > 0.05$).

Striatal SBRs correlated negatively with age in both groups, positively with the MMSE score in both groups and negatively with the MDS-UPDRS motor score in PD patients (Supplementary Table 1). However, there were no significant correlations between striatal SBRs and NMSS total scores in either group (Supplementary Table 1). Adjusting for age, UPDRS motor score or MMSE score did not change the results ($p > 0.05$). In the voxel-wise whole brain analysis of PD patients, there was no significant association between SBR and NMSS total score.

The results remained the same when PD patients were compared to patients with ET ($p > .05$). Out of 84 PD patients and 109 DAT-normal patients, 25 (30%) and 8 patients (7%), respectively, were receiving antiparkinsonian medications at the time of imaging. The results remained the same when these patients were removed from the analysis (NMSS total scores mean [SD] 56.1 [45.7] vs 72.8 [52.7], corrected $p = .26$). In addition, there were no differences in NMSs between PD

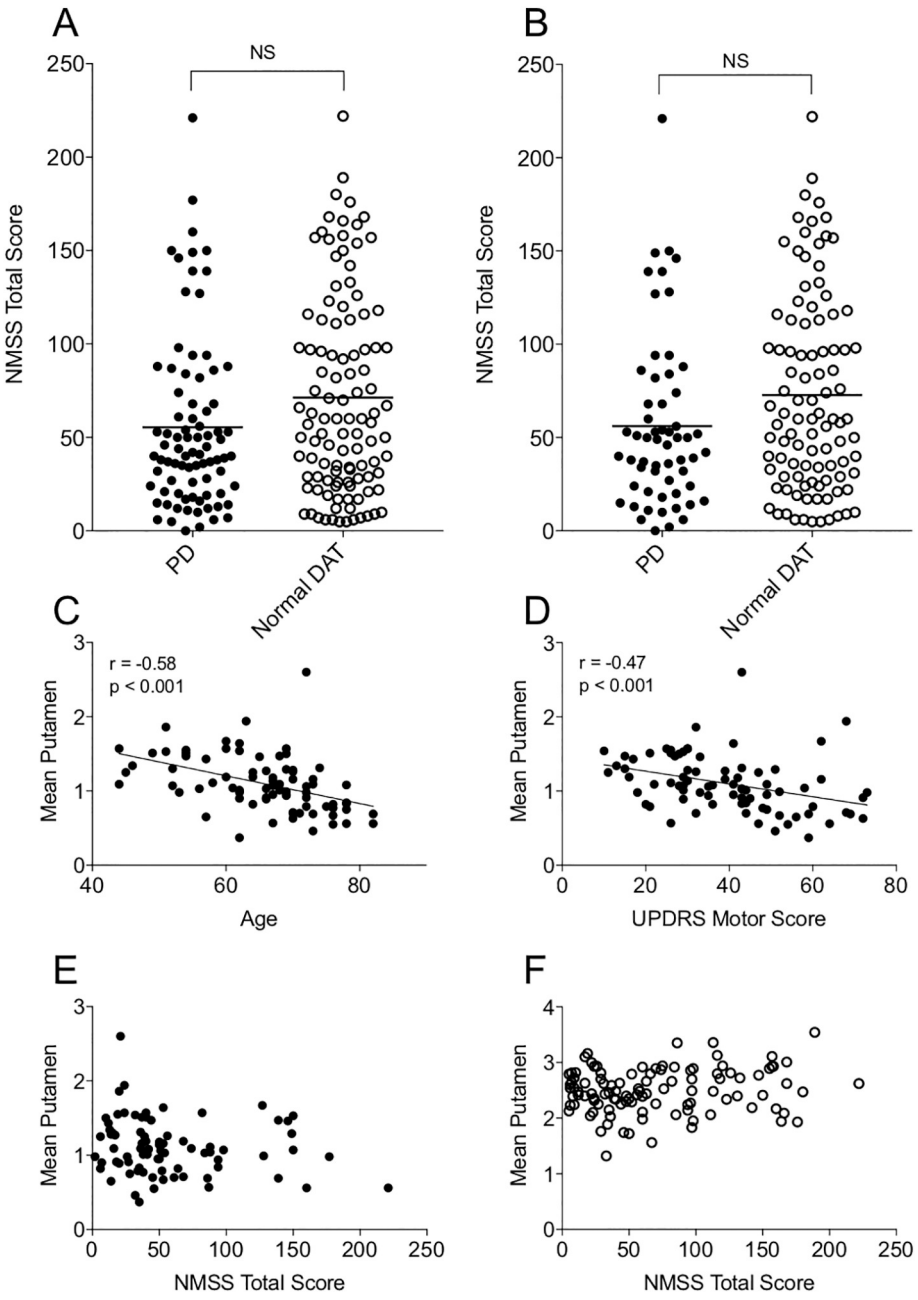

Fig. 1. A. NMSS total score in PD patients and normal DAT patients. B. NMSS total score in patients with no dopaminergic medication. Relationship between mean putamen SBR and C. age in PD patients, D. MDS-UPDRS motor score in PD patients, E. NMSS total score in PD patients and F. NMSS total score in normal DAT patients. DAT = dopamine transporter, NMSS = Non-motor symptoms scale, NS = Not significant, MDS-UPDRS = the Movement Disorder Society Unified Parkinson's Disease Rating Scale, PD = Parkinson's disease.

patients with and without antiparkinsonian medications (NMSS total scores mean [SD] 54.0 [47.8] vs 56.1 [45.7], corrected p = 1.0).

4. Discussion

Our results show that the total burden of NMSs is equal between PD patients and patients with similar motor symptoms but normal brain dopamine function. NMS burden was also not associated with brain dopamine function in PD patients who were mostly unmedicated and at early stages of their disease.

Previous studies have demonstrated that NMSs are more prevalent in PD than in healthy controls [7]. The current study is the first to investigate NMS burden in patients with parkinsonism of uncertain cause. Our results are supported by findings derived from the Parkinson's Progression Markers Initiative (PPMI) cohort demonstrating that the prevalence of NMSs is the same or higher in subjects with SWEDDs compared to PD patients with the exception of hyposmia [6,8]. In our study, the only NMSS subscores that differed between PD and DAT-normal patients were related to dysfunctions in perception and attention/memory, which were more common in DAT-normal patients. The reason for this finding is unclear and needs further verification, but the differences in subjective cognitive symptoms may partially be related to the finding that PD patients with mild cognitive impairment do not appear to correctly identify cognitive deficits that they have [9]. Previous studies support also the finding that DAT density is not associated with total NMS burden in PD [7,10]. Given that the NMSS total score is a sum score (severity and frequency) of various symptoms that likely do not have the same pathophysiological

basis, the present study cannot be interpreted to indicate that individual NMSs are not dopamine dependent. Additionally, neurotransmitters other than dopamine are involved in NMSs [1], and further studies using different neurotransmitter ligands are needed to investigate this issue in full. In addition, it should be noted that the definition of the total NMS burden may not be the same in all studies. We defined the total burden as the NMSS total score, whereas there are previous studies that have used the number of different NMSs as the indicator of the total NMS burden [11].

It should be noted that our PD patients had shorter motor symptom durations than the controls. This finding is consistent with earlier studies [12], and the motor symptom duration did not correlate with total NMSS score. The MDS-UPDRS part III (motor part) scores did not differ between the two groups, a finding which may seem counterintuitive at first glance. It is important to note, however, that DAT normal patients were not healthy although they turned out to have normal DAT binding. Instead, they had motor symptoms to the degree that they were suspected to have PD and were referred for SPECT. Furthermore, MDS-UPDRS was developed for PD, and the results concerning other conditions may not reflect motor symptoms as accurately as in PD. We have discussed some of these issues in our earlier report as well [13]. In the interpretation of our results it is also important to note that the study population included patients who were referred for DAT imaging due to diagnostic uncertainty. Thus, although the sample reflects clinical reality at SPECT imaging, it may not be representative of the typical clinical population of patients with PD. Nevertheless, the total NMSS scores in our PD patients were very similar to those reported in previous NMSS PD studies [10,11], which suggests that the NMSS burden in our PD patients was not particularly high or low. However, in all NMSS studies, recall bias is a possible common source of error because NMSS focuses on the non-motor symptoms during the previous month. It is also noteworthy that we used a single-question screen for RBD, and although it appears to provide a sensitive estimate of RBD diagnosis [14], RBD can be most accurately diagnosed by full polysomnography [15].

The findings of this study confirm that NMSs are prevalent in PD. More importantly, they indicate that, as compared to PD patients, the burden of NMSs is similar in clinically matched population of patients without neurodegenerative parkinsonism syndromes. Total NMS load thus does not seem to be useful for differential diagnostics and the results do not support a significant relationship between presynaptic dopamine function and NMS burden. It is apparent that clinical NMS screening is important also in patients with parkinsonism/tremor who have normal brain dopamine function. The present findings also highlight the importance of control population selection in PD NMS-trials when making inferences for clinical practice.

Funding

This study was supported by the Finnish Parkinson Foundation, The Finnish Medical Foundation, The Päivikki and Sakari Sohlberg Foundation, The Academy of Finland (295724, 310835), the Turku University Foundation and Turku University Hospital (ERVA-funds). Elina Jaakkola was supported by the Finnish Parkinson Foundation and the Finnish Cultural Foundation. Juho Joutsa was funded by The Academy of Finland (grant #295580), The Finnish Medical Foundation and the Orion Research Foundation and has received travel grants from Abbvie and Orion. Elina Mäkinen was supported by the Finnish Parkinson Foundation and the Turku University Foundation. Tommi Noponen, Miia Pitkonen, Reeta Levo and Tuomas Mertsalmi: no funding. Filip Scheperjans was funded by The Finnish Medical Foundation and The Academy of Finland (295724, 310835). Valtteri Kaasinen was funded by The Päivikki and Sakari Sohlberg Foundation, the Turku University Foundation and Turku University Hospital (ERVA-funds) and has received travel grants from Orion Pharma and Nordic Infucare.

Declaration of Competing Interest

None.

Acknowledgements

The staff of the Department of Nuclear Medicine, Turku University Hospital, Finland, is gratefully acknowledged.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.07.025.

References

[1] A.H.V. Schapira, K.R. Chaudhuri, P. Jenner, Non-motor features of Parkinson disease, Nat. Rev. Neurosci. 18 (2017) 509.
[2] P. Martinez-Martin, C. Rodriguez-Blazquez, M.M. Kurtis, K.R. Chaudhuri, Group NV, The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease, Mov. Disord. 26 (2011) 399–406.
[3] J. Seubert, E.J. Laukka, D. Rizzuto, et al., Prevalence and correlates of olfactory dysfunction in old age: a population-based study, J. Gerontol. A Biol. Sci. Med. Sci. 72 (2017) 1072–1079.
[4] M. Giorelli, J. Bagnoli, L. Consiglio, et al., Do non-motor symptoms in Parkinson's disease differ from essential tremor before initial diagnosis? A clinical and scintigraphic study, Parkinsonism Relat. Disord. 20 (2014) 17–21.
[5] M.A. Qamar, A. Sauerbier, M. Politis, H. Carr, P. Loehrer, K.R. Chaudhuri, Presynaptic dopaminergic terminal imaging and non-motor symptoms assessment of Parkinson's disease: evidence for dopaminergic basis? NPJ Park. Dis. 3 (2017) 5.
[6] F.S. Sprenger, K. Seppi, A. Djamshidian, et al., Nonmotor symptoms in subjects without evidence of dopaminergic deficits, Mov. Disord. 30 (2015) 976–981.
[7] T. Simuni, C. Caspell-Garcia, C.S. Coffey, et al., Baseline prevalence and longitudinal evolution of non-motor symptoms in early Parkinson's disease: the PPMI cohort, J. Neurol. Neurosurg. Psychiatry 89 (2018) 78–88.
[8] S. Taylor, J. Gafton, B. Shah, et al., Progression of nonmotor symptoms in subgroups of patients with non-dopamine-deficient parkinsonism, Mov. Disord. 31 (2016) 344–351.
[9] J.N. Copeland, A. Lieberman, S. Oravivattanakul, A.I. Tröster, Accuracy of patient and care partner identification of cognitive impairments in Parkinson's disease-mild cognitive impairment, Mov. Disord. 31 (2016) 693–698.
[10] S.B. Park, K.Y. Kwon, J.Y. Lee, et al., Lack of association between dopamine tranporter loss and non-motor symptoms in patients with Parkinson's disease: a detailed PET analysis of 12 striatal subregions, Neurol. Sci. 40 (2019) 311–317.
[11] K.R. Chaudhuri, A. Sauerbier, J.M. Rojo, et al., The burden of non-motor symptoms in Parkinson's disease using a self-completed non-motor questionnaire: a simple grading system, Parkinsonism Relat. Disord. 21 (2015) 287–291.
[12] E. Jaakkola, J. Joutsa, V. Kaasinen, Predictors of normal and abnormal outcome in clinical brain dopamine transporter imaging, J. Neural Transm. (Vienna) 123 (2016) 205–209.
[13] E. Mäkinen, J. Joutsa, E. Jaakkola, et al., Individual parkinsonian motor signs and striatal dopamine transporter deficiency: a study with [I-123]FP-CIT SPECT, J. Neurol. 266 (2019) 826–834.
[14] R.B. Postuma, I. Arnulf, B. Hogl, et al., A single-question screen for rapid eye movement sleep behavior disorder: a multicenter validation study, Mov. Disord. 27 (2012) 913–916.
[15] Y. Liu, X.Y. Zhu, X.J. Zhang, S.H. Kuo, W.G. Ondo, Y.C. Wu, Clinical features of Parkinson's disease with and without rapid eye movement sleep behavior disorder, Transl. Neurodegener. 6 (2017) 35.