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Original Article

Non-motor symptoms in a Flanders-Belgian population of 215 Parkinson's disease patients as assessed by the Non-Motor Symptoms Questionnaire

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Abstract: Background: Non-motor symptoms (NMS) in Parkinson's disease (PD) are frequent, increase the patients' disability and have an important negative impact on their quality of life. Methods: We used a Dutch translation of the Non-Motor Symptoms Questionnaire (NMSQuest) to identify NMS in a population of 215 Belgian PD patients. Results: A median number of 8 NMS was reported per patient. Urinary urgency (59.2 %), nocturia (56.9 %), insomnia (45.8 %), attention problems (45.5 %) and orthostatism (41.2 %) were the most frequently denoted NMS. A higher number of NMS was present with more severe Hoehn and Yahr stages. Longer disease duration was associated with more NMS. Furthermore, clinical markers of disease progression were also associated with a higher number of NMS. However, early-onset patients (< 50 years) reported less NMS than late-onset patients after correction for disease duration. Interestingly, in early-onset patients we observed more unexplained pain and more hyperhydrosis. Conclusion: We confirm the high prevalence of NMS in PD patients. A long disease duration and more severe disease are associated with a higher number of NMS. Importantly, even if late-onset patients generally report more NMS, unexplained pain and hyperhydrosis are more frequent in early-onset patients.

Keywords: Parkinson's disease, non-motor symptoms, NMSQuest, questionnaire

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative brain disorder with a prevalence of 1,8% in subjects older than 65 years [1]. An age-dependent increase in prevalence to approximately 4% is noted in subjects older than 85 years [2]. Classically, the clinical description of PD was focused on 4 cardinal symptoms: bradykinesia, rigidity, resting tremor and postural instability [3]. Clinical diagnostic criteria for PD still rely on the presence of these motor symptoms, together with a therapeutic response to levodopa and the absence of atypical features [4,5]. During many years, research on PD was mainly focused on motor symptoms and motor complications. More recently, the importance of non-motor symptoms and their impact on quality-of-life of PD patients was recognized [6]. Data from the Sydney Multicentre Study, in which a cohort of PD patients was followed during 20 years, demonstrated that at 15 and 20 years from baseline non-motor symptoms predominate suggesting problems related to NMS occur in late PD [7,8]. The impact and prevalence of NMS in early PD remains unclear and the general perception is that early PD is associated with a low burden of NMS. Chaud-

huri and associates developed a brief self-administered questionnaire (NMSQuest) to screen for the presence of 30 non-motor symptoms [9]. We developed a Dutch translation of the questionnaire and report in this paper the results obtained in a population of 215 Flanders -Belgian PD patients.

Material and methods

Study population

We have recruited PD patients after obtaining their informed consent in outpatient clinical neurology departments or through collaboration with patient support groups. Patients were consecutively included in the study only if they fulfilled the NINDS clinical diagnostic criteria for 'probable' or 'possible' PD [4]. When available, additional clinical information (magnetic resonance imaging, nuclear imaging, laboratory studies) was assessed to ascertain the clinical diagnosis. The majority of the patients were examined by D.C. As these patients were recruited to participate in a larger study on genotype-phenotype correlations in PD, a comprehensive clinical protocol was followed to collect a large dataset of clinical features of each patient, including onset age, familial history, medication history, presence of levodopa-related motor complications, Unified Parkinson's Disease Rating Scale (UPDRS) motor score, Hoehn and Yahr (HY) stage and Mini-Mental State Examination (MMSE). Probable PD dementia was diagnosed using the algorithm of the MDS Task force on Dementia in PD [10]. Patients with fluctuations were assessed and responded to the NMSQuest in 'on' state. The questionnaire was completed in more than 85% of cases by the patient. If cognitive or motor problems impeded this activity, help of a family member or caregiver was allowed. This study was approved by the ethical board of the Antwerp University Hospital and the University of Antwerp.

Non-motor symptoms questionnaire

We generated a Dutch translation of the original Non-Motor Symptoms Questionnaire (NMSQuest) [9] and validated it using a translation-backtranslation protocol. The English questionnaire was translated to Dutch and subsequently, this Dutch translation was back-translated to English independently by two individuals. The original English questionnaire was compared with the two back-translated questionnaires and discrepancies were corrected by consensus between the three people involved in the translation. A pilot study using the Dutch NMSQuest was conducted in 47 PD patients [11].

Statistical methods

Statistical analyses were conducted using the software program PASW Statistics version 18 (SPSS inc.). All positive responses ("yes") on the NMSQuest were summed for each patient (NMS score). That score indicates the number of declared NMS and has been used in previous publications [9,12,13]. Non-parametric statistical tests were performed to compare group distributions (Mann-Whitney U and Kruskal-Wallis test) with a threshold for significance being set at $p < 0.05$. Frequencies were compared using Pearson's chi-square test with similar threshold. Correlations were assessed using the Spearman rank correlation coefficient (r_S). The number of NMS in two patient groups (young vs. old and early-onset vs. late-onset) was compared by performing a loglinear Poisson regression model in which disease duration was added as independent covariate. The frequency of each NMS in both groups was compared with use of a binary logistic regression model in which disease duration was also added as independent covariate.

Results

The Dutch NMSQuest in this study was completed by 215 PD patients with a mean age of 67.1 (range: 36-88) and disease duration of 7.3 years (range: 1-30). All HY stages were represented in the study population with a higher proportion of mild PD (HY stage 1 and 2). Further demographic and clinical characteristics of the study participants are presented in **Table 1**. Parkinson's disease dementia fulfilling the above-mentioned criteria, was present in 10.4% of the patients and generally these patients suffered from mild to moderate cognitive deterioration (MMSE: 20.5 ± 3.5). Most of the patients (n=172) were recruited in two outpatient clinical neurology departments [Antwerp University Hospital (n= 123) and ZNA Middelheim and Hoge Beuken Hospital (n=49)], the remainder of patients (n=43) were invited to participate in collaboration with patient support organizations. We divided the total population in two sub-

Table 1. Demographic and clinical variables of total study population and early-onset (< 50 y) and late-onset (≥ 50 y) subgroups

	Total	Early-onset group	Late-onset group	p-value
Total number	215	46	169	-
M/F ratio	1.59	3.18	1.35	0.026
Age (years)	67.1 ± 10.4	54 ± 9.3	70.6 ± 7.5	<0.001
Onset age (years)	59.8 ± 11.6	43.1 ± 6.5	64.3 ± 7.9	<0.001
Disease duration (years)	7.3 ± 6.3	10.9 ± 7.9	6.3 ± 5.4	<0.001
Median HY stage	2 (1-5)	2 (1-4)	2 (1-5)	-
Mean UPDRS motor score	25 ± 13.8	22.9 ± 13.1	25.5 ± 13.9	0.269
Resting tremor	62.9%	47.4%	66.9%	0.038
Postural instability	24.8%	16.3%	27%	0.168
Motor fluctuations	43.8%	57.8%	39.9%	0.041
Dyskinesias	26.8%	46.7%	21.3%	0.001
Dementia	9.6%	11.6%	8.9%	0.564
Levodopa therapy	79.6%	73.3%	81.4%	0.295
Dopamine-agonist therapy	36.8%	46.7%	34%	0.161

P-values were calculated using Mann-Whitney U test for continuous variables and Pearson's chi square for binary variables.

groups: early-onset PD (onset age < 50 years; n=46) and late-onset PD (onset age ≥ 50 years; n=169). Patients in the early-onset group exhibited a longer disease duration (Mann-Whitney U test, p < 0.001) and more motor fluctuations (Pearson' s chi square, p=0.041) and dyskinesias (Pearson's chi square, p=0.001 and see **Table 1**).

The majority of the 30 questions were completed by all patients, except for questions 18 and 19 (asking about libido problems and sexual dysfunction) showing a considerable number of missing values (in respectively 15% and 25% of the total patient group). The most frequently reported NMS in the total study population were urinary urgency (59.2 %), nocturia (56.9 %), insomnia (45.8 %), attention problems (45.5 %) and dizziness (41.2 %). The frequency of NMS across the different HY stages is indicated in **Table 2**. A median number of 8 NMS (interquartile range: 8; limits: 0-24) was reported per patient. More advanced disease, as indicated by a higher HY stage, was associated with a significant higher number of reported NMS (Kruskal-Wallis test, p<0.001 and see **Figure 1**). Also, more NMS were noted in patients with longer disease duration (Kruskal-Wallis test, p<0.001 and see **Figure 1**). Interestingly, the mean number of reported NMS was similar for a disease duration of 10-14.9 years and of ≥15 years (Mann-Whitney U test, p=0.841). Clinical features associated with disease severity, such as presence of motor fluctuations (Mann-Whitney U test, p<0.001), dyskinesias (Mann-Whitney U test, p=0.001), postural instability (Mann-Whitney U test, p<0.001), hallucinations (Mann-Whitney U test, p<0.001) or dementia (Mann-Whitney U test, p<0.001) were also associated with a higher NMS score. A moderate, but significant correlation was observed between the UPDRS motor score and the NMS score (r_S=0.367; p<0.001). Furthermore, onset age (r_S =-0.065; p=0.352) or age at inclusion (r_S=0.127; p=0.063) were not correlated with the NMS score. Patients with age ≥ 65 years did not report significantly more NMS than younger patients (loglinear Poisson regression after correction for disease duration , p=0.451). However, in the early-onset group (onset age < 50 years) we observed a smaller number of NMS (odds ratio (OR): 0.857; 95% confidence interval (CI): 0.763 - 0.962) than in the late-onset patients (onset age ≥ 50 years) after correction for disease duration, as calculated using loglinear Poisson regression. Interestingly, after correction for disease duration early-onset patients reported more unexplained pain (OR: 2.475; 95% CI: 1.096 - 5.590), more hyperhydrosis (OR: 2.351; 95 % CI: 1.123 -4.925), less

Table 2. Number and percentage of patients experiencing each NMS

		Total N=215		HY 1 N=54		HY 2 N=99		HY 3 N=35		HY 4 + 5 N=21	
Q	Symptom	n	%	n	%	n	%	n	%	n	%
1	dribbling	84	39.3	8	14.8	42	42.9	17	48.6	14	66.7
2	taste/smelling	87	40.5	19	35.2	41	41.4	18	51.4	7	33.3
3	swallowing	64	29.9	12	22.2	27	27.6	13	37.1	11	52.4
4	vomiting	26	12.1	6	11.1	14	14.1	4	11.8	2	9.5
5	constipation	83	38.6	18	33.3	36	36.4	16	45.7	11	52.4
6	bowel incontinence	7	3.3	2	3.7	2	2.0	1	2.9	1	4.8
7	bowel emptying incomplete	46	21.6	14	25.9	20	20.2	8	23.5	3	15.0
8	urinary urgency	125	59.2	27	50.0	57	57.6	24	68.6	14	82.4
9	nocturia	119	56.9	23	43.4	57	58.2	23	67.6	11	61.1
10	pains	39	18.2	13	24.1	17	17.2	4	11.4	15	75.0
11	weight	33	15.3	8	14.8	15	15.2	4	11.4	5	23.8
12	remembering	81	37.9	17	32.1	32	32.3	18	51.4	13	61.9
13	loss of interest	70	32.6	16	29.6	29	29.3	11	31.4	11	52.4
14	hallucinations	38	17.7	3	5.6	12	12.1	11	31.4	12	57.1
15	concentrating	97	45.5	24	44.4	36	36.4	17	51.5	17	81.0
16	sad, blues	83	38.6	17	31.5	39	39.4	14	40	11	52.4
17	anxiety	66	30.7	13	24.1	27	27.3	11	31.4	12	57.1
18	sex drive	63	34.4	14	27.5	31	34.4	7	28	8	72.7
19	sex difficulty	62	38.5	14	30.4	32	39.5	8	42.1	7	70.0
20	dizzy	87	41.2	19	35.8	36	36.7	21	61.8	10	50.0
21	falling	59	27.6	2	3.7	23	23.5	18	51.4	15	71.4
22	daytime sleepiness	62	29	7	13.0	28	28.6	14	40	12	57.1
23	insomnia	98	45.8	23	42.6	43	43.9	17	48.6	13	61.9
24	intense vivid dreams	61	28.6	13	24.1	27	27.6	10	29.4	10	47.6
25	acting out during dreams	72	34.8	14	28.0	26	26.8	10	29.4	10	50.0
26	restless legs	69	32.4	13	24.1	25	25.5	19	54.3	10	50.0
27	swelling legs	58	27	8	14.8	23	23.2	15	42.9	10	47.6
28	sweating	52	24.2	12	22.2	22	22.2	7	20	10	47.6
29	diplopia	35	16.4	6	11.1	9	9.1	15	42.9	5	25.0
30	delusions	13	6	3	5.6	3	3.0	4	11.4	5	23.8

HY: Hoehn and Yahr staging (not available for 6 patients). Q: question number. Conflicting number of NMS and respective percentage are due to missing values.

drooling (OR: 0.355; 95% CI: 0.161 - 0.785), less urinary urgency (OR: 0.367; 95% CI: 0.178 - 0.759), less orthostatism (OR: 0.334; 95% CI: 0.151 - 0.738) and less falls (OR: 0.217; 95% CI: 0.079 - 0.594) in comparison with late-onset patients.

The NMSQuest can be subdivided in nine subdomains [12]. The percentage of positive answers for each subdomain was calculated to allow comparisons, because the number of items varies between the different subdomains. The subdomains with the highest mean percentage of positive answers in the total population were: urinary symptoms (57.7%), apathy/attention/memory (38.7%), cardiovascular symptoms (36.4%) and sexual function (34.8%). A significant higher subdomain score was observed in patients with a more advanced disease (based on HY stage) for eight subdomains; only depression/anxiety did not show an increased prevalence across higher HY stages (Kruskal-Wallis test, p= 0.054) (see **Figure 2**).

Discussion

We have used a Dutch translation of the NMSQuest in this study to identify self-reported non-motor symptoms in a population of 215 Flanders-Belgian PD patients. The key results of

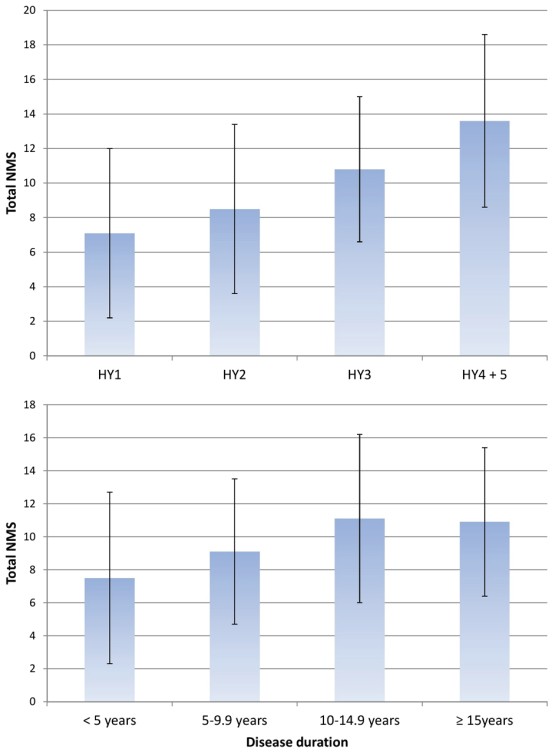

Figure 1. Total number of NMS, Hoehn and Yahr stage and disease duration. The increase in number of NMS with higher Hoehn and Yahr stage is shown. Longer disease duration is associated with increased NMS stabilizing after 10 years of disease duration. Number of patients in each disease duration interval: < 5 years: 94; 5-9.9 years: 55; 10-14.9 years: 38; 15-19.9 years: 27; missing: 1. Abbreviations: HY 1: Hoehn and Yahr stage 1; HY 2: Hoehn and Yahr stage 2; HY 3: Hoehn and Yahr stage 3; HY 4 + 5: Hoehn and Yahr stage 4 and 5: Total NMS: total number of non-motor symptoms.

this study confirm the high burden of NMS in PD as suggested in previous studies using the same questionnaire. We report that the prevalence of NMS was higher in late-onset PD and furthermore, at 10 years of motor disease, the burden of NMS ceases to increase significantly and there appears to be a "tailing off" of the number of NMS.

The response rate for the different questions of the NMSQuest was excellent, except for the questions about sexual dysfunction, which were

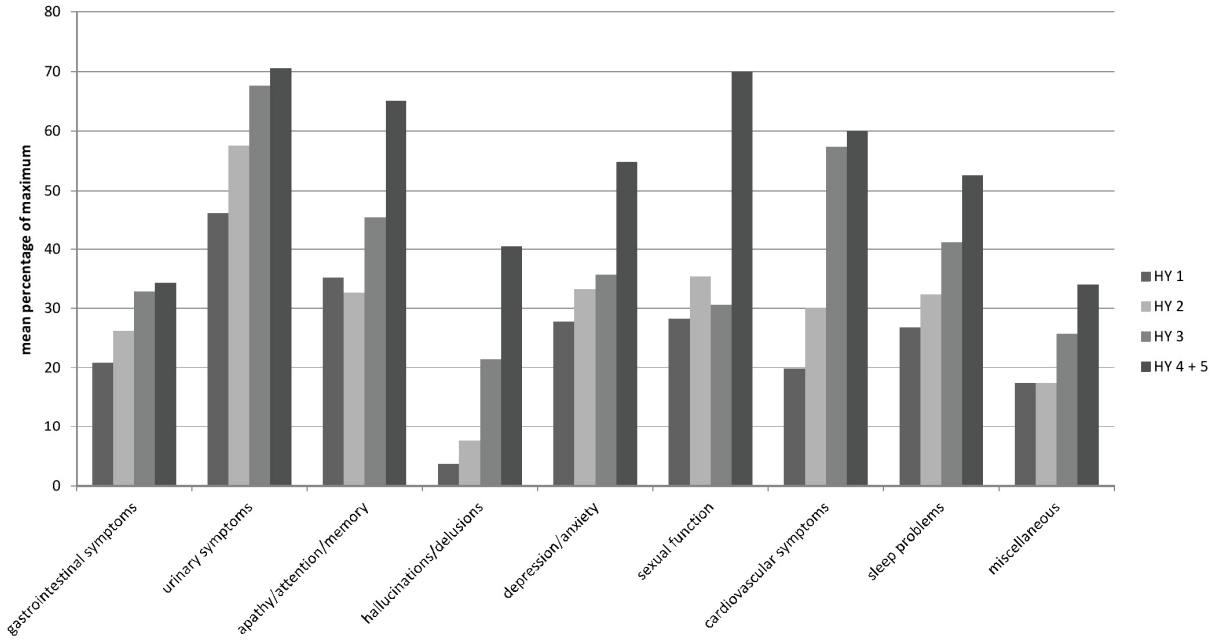

Figure 2. Subdomains of NMSQuest across different Hoehn and Yahr stages. The mean percentage of positive answers on all questions of a subdomain of the NMSQuest is shown across different Hoehn and Yahr stages. Abbreviations: HY 1: Hoehn and Yahr stage 1; HY 2: Hoehn and Yahr stage 2; HY 3: Hoehn and Yahr stage 3; HY 4 + 5: Hoehn and Yahr stage 4 and 5. The respective p-values of the Kruskal-Wallis test for each domain are: gastrointestinal symptoms: 0.014; urinary symptoms: 0.039; apathy/attention/memory: 0.006; hallucinations/delusions: <0.001; depression/anxiety: 0.054; sexual function: <0.028; cardiovascular symptoms: <0.001; sleep problems: 0.003; miscellaneous: <0.016.

not answered by or not applicable for a considerable number of study participants. The older age of study participants encompassing the increased prevalence of widows, the reduced sexual activity in this age group and uncomfortable feelings about these questions were already suggested by others as reasons for these incomplete responses [9]. The most frequently reported NMS in the total study population were highly similar to other studies using the NMSQuest [9,12]. Urinary symptoms and insomnia were very common in PD patients, but numerous other NMS (attention problems, orthostatism, hyposmia, dribbling, constipation, depression, sexual problems, memory problems, REM sleep behavior disorder, apathy, restless legs and anxiety) were reported by at least 30 % of the patients. We observed a significant increase in the number of NMS with advancing motor disease as indicated by the HY stage. Longer disease duration was also associated with a greater burden of NMS, however interestingly, in patients with more than ten years of disease duration, the number of NMS appeared to plateau off. In a cohort of 886 PD patients, NMS load was associated with increasing disease duration [14]. However, some NMS such as loss of taste/smell, loss of interest and apathy were not more frequent in patients with longer disease duration, suggesting that some NMS are already present early in the disease, while others appear later. This could possibly explain in our data the plateau of the NMS score at group level after ten years of disease duration. Little data is available about the natural history of the load of NMS in PD, and it is likely that there are differential progression rates between the range of NMS documented in the NMSQuest. Interestingly, we did not observe a higher NMS score in older patients, contrary to a previous report [12]. Importantly, we also noted that mild PD patients (according to motor staging with Hoehn and Yahr 1-2) in our sample registered considerable number of NMS suggesting the need for specific assessment of NMS in the holistic care of PD. This is important as in a study of 750 mild PD patients, NMS were shown to independently predict health-related quality of life [15].

In our study, a higher number of NMS was reported by late-onset patients, but two NMS (unexplained pain and hyperhydrosis) were significantly more prevalent in the early-onset group. Greater reporting of urinary problems, orthostatism and falls in the late-onset group could be related to the increased prevalence of other comorbid (e.g. urological, cardiovascular and orthopedic) diseases with older age as well as autonomic dysfunction. The frequent and early development of dystonia and dyskinesias (which can be painful) in early-onset patients could possibly account for the higher proportion of patients reporting pain in this group and pain has been reported in early PD and even preceding the motor onset of PD [16]. Also, the higher proportion of motor fluctuations together with more frequent dyskinesias in the early-onset group could explain that these patients experience more hyperhydrosis since excessive sweating mainly occurs during 'off' periods and in 'on' state with dyskinesias [17].

This study has drawbacks which include the fact that an effect of medication-induced fluctuations of NMS (non-motor fluctuations) cannot be excluded [18]. As for logistic reasons, questionnaires were completed in the 'on' state. In the future, the questionnaire response could for instance be improved by asking for each symptom if there is improvement after taking a medication dose. Furthermore, another possible limitation of our study lies in the significantly longer disease duration in the early-onset group, which could be a source of bias. Therefore, the comparisons between the early- and late-onset groups were corrected for disease duration. Like in any observational study of this kind, we cannot rule out the contribution of comorbidity to the genesis of the observed NMS. However, the NMSQuest was primarily designed as a screening questionnaire and is not suited for measurement of NMS severity or for follow-up studies [9]. For this purpose, the Non-Motor Symptom Scale (NMSS) has been developed, which requires a trained observer to score the frequency and severity of NMS [19].

We used a Dutch translation of the NMSQuest in a population of 215 PD patients and obtained similar results as other research groups [9,12,13]. We corroborate the increasing number of NMS with longer disease duration and more severe disease, also observed in the PRIAMO study. Interestingly, in the PRIAMO study, the most frequently detected NMS were psychiatric symptoms, sleep and gastro-intestinal problems [20]. The discrepancies can probably be explained by methodological differences as a more extensive semistructured interview was performed to detect NMS in the PRIAMO study.

In a recent study, Romenets and coworkers used a clinical gold-standard evaluation to detect the presence of the 30 NMS that are investigated in the NMSQuest [21]. Nocturia (78.3%), urinary urgency (77.9%) and insomnia (66.7%) were among the most prevalent NMS, showing an even higher prevalence than in our study. Specificity for most NMSQuest items was rather high, while sensitivity was variable with only five items reaching a sensitivity of more than 0.80. The mean sensitivity was improved if only NMSQuest items with an important impact on the patient's quality of life were included in the analysis, indicating that the NMSQuest can serve as valuable screening questionnaire in the detection of clinically meaningful NMS in PD.

Finally, we advocate for an increased awareness of NMS among the health care workers and patients. An important proportion of NMS is not spontaneously declared by PD patients to their health care providers [13]. The systematic use of questionnaires can draw attention to these symptoms, many of which can be adequately treated or at least alleviated [22,23]. Also, patients and their relatives are often unaware of the relation between the experienced NMS and PD, indicating a need for improved patient education [24].

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Declaration of conflicts of interest

The authors report no conflicts of interest.

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