RESEARCH PAPER

Non-motor symptoms in early Parkinson's disease: a 2-year follow-up study on previously untreated patients

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ABSTRACT

Background Non-motor symptoms are very common among patients with Parkinson's disease since the earliest stage, but little is known about their progression and their relationship with dopaminergic replacement therapy.

Methods We studied non-motor symptoms before and after 2 years from dopaminergic therapy introduction in ninety-one newly diagnosed previously untreated PD patients.

Results At baseline, nearly all patients (97.8%) referred at least one non-motor symptom. At follow-up, only few non-motor symptoms significantly changed. Particularly, depression and concentration became less frequent, while weight change significantly increased after introduction of dopamine agonists.

Conclusions We reported for the first time a 2-year prospective study on non-motor symptoms before and after starting therapy in newly diagnosed PD patients. Even if non-motor symptoms are very frequent in early stage, they tend to remain stable during the early phase of disease, being only few non-motor symptoms affected from dopaminergic therapy and, specifically, by the use of dopamine agonists.

INTRODUCTION

Non-motor symptoms (NMS) are very common among patients with Parkinson's disease (PD) since the earliest stage.[1 2] Identification and management of NMS have been recognised by the UK National Institute for Clinical Excellence as an important unmet need in PD.[3] In fact, although NMS negatively affect the patient's quality of life and significantly contribute to hospitalisation at an advanced disease stage,[4 5] they are under-recognised and undertreated in clinical practice.

It has been clearly reported that prodopaminergic therapy improves motor symptoms and quality of life in patients with PD.[6] Little is known about the effect of dopamine replacement therapy on NMS: it has been reported that it only partly improves some NMS, such as depression, bladder function, pains and sleep,[7–10] suggesting NMS impairment is variably driven by dopaminergic denervation. Furthermore, other NMS, such as orthostatic hypotension, nausea, sleep disturbances, hallucinations or psychosis may arise or worsen consequent to dopaminergic replacement during the course of disease.[11 12] It has also been reported that 15 years after PD diagnosis, patients mainly suffered from non-dopaminergic symptoms such as falls and dysarthria, and also cognitive impairment, daytime somnolence and urinary incontinence.[13]

However, these evidences came from studies with cross-sectional design or a short-term prospective observation period. Moreover, interpretation of these results is limited by the lack of a validated tool for detection on NMS in PD, and by the scarce amount of data on NMS rate of progression since the earliest stage, before patients are treated.

In the present study, we report for the first time a 2-year prospective assessment of NMS before and after starting dopaminergic therapy in a large cohort of newly diagnosed PD patients.

PATIENTS AND METHODS

Study design

We conducted a baseline evaluation to determine the prevalence of NMS in a cohort of newly diagnosed untreated PD patients. Due to the observational nature of our study, dopaminergic therapy was started according to the discretion of each supervising physician. After 2 years from baseline, we conducted a follow-up evaluation of NMS, as described below. The study was approved by the local ethics committee, and all patients provided written informed consent.

Data collection and methods

All the PD patients included in this study were prospectively included in an ongoing research project conducted at the movement disorder centre, University Federico II of Naples, Italy, between May 2008 and June 2009. Inclusion and exclusion criteria have been extensively described elsewhere.[14] In brief, inclusion criteria were (1) the presence of parkinsonian syndrome according to UK Parkinson's Disease Society Brain Bank Diagnostic Criteria, (2) disease duration <2 years and (3) no history of present or past therapy with prodopaminergic agents. Additional criteria for inclusion were lack of significant cerebral lesions on MRI or CT, or severe concomitant disease that might explain the presence of neurological or psychiatric disturbances. None of the patients were treated with anticholinergic agents, choline esterase

inhibitors, antidepressants, anxiolytic drugs, or other centrally acting substances.

Detailed clinical information was obtained from the patient's history and neurological examination. Parkinsonism was diagnosed by movement disorders specialists experienced in parkinsonian disorders. The Unified Parkinson's Disease Rating Scale III (UPDRS-III) was used to evaluate motor disability.[15] All patients completed the Non-Motor Symptoms Questionnaire (NMSQuest), a validated tool for detection of NMS in PD.[16] Patients (and care-givers) were asked to report specific symptoms as 'present/absent' with reference to the month before the visit.

At least 2 years after enrolment, a clinical evaluation was performed to confirm the clinical diagnosis of PD according to response to the dopaminergic therapy and exclusion of atypical symptoms/signs.[17] Motor disability was evaluated by mean of UPDRS-III and NMS checked by the NMSQuest, as at baseline. Dopaminergic treatment was recorded by means of drug class, daily dosage and therapy duration. L-Dopa-equivalent daily dosage (LEDD) was calculated for each drug, and the total LEDD reported, as previously suggested.[18] Patients taking drugs other than dopamine agonists (DA), mono-amino-oxidase inhibitors type-B (IMAO), and L-Dopa were excluded from the analyses.

Statistical analysis

Only fully completed scales were used for statistical analysis. The proportion of patients referring each NMS was calculated at baseline and follow-up visit. The evolution of each NMS was evaluated by mean of 'percentage change': that is (new percentage—old percentage)/old percentage. Differences in NMS frequency between baseline and follow-up were checked by McNemar test on paired proportions. Correlations between NMS and therapy by mean of drug class, therapy duration, DA-LEDD, IMAO-LEDD, L-Dopa dosage and total-LEDD, were checked in the whole cohort through the Spearman's rank test. The significance threshold was set to 0.05 with Bonferroni's correction. Finally, multiple logistic regression analyses with forward stepping (likelihood ratio method) were applied. NMS attaining a significance level in the bivariate analysis were included in a subsequent multivariate logistic regression model, using therapy data as independent variables, and sex, age, disease duration and motor disability by mean of UPDRS III as nuisance (covariate of non-interest).

Statistical analyses were done with the STATA software, V.11.0 (StataCorp LP).

RESULTS

We enrolled 116 de-novo untreated parkinsonian patients. At follow-up, we excluded 25 patients from the analysis: nine patients due to a diagnosis other than PD (namely, three multiple system atrophy, one progressive supranuclear palsy, one corticobasal syndrome, one Lewy body dementia, three PD dementia); 13 patients were taking drugs other than prodopaminergic (specifically, five sertraline, four amantadine, two clonazepam, one alprazolam and one quetiapine); and three patients withdrew their consent. Thus, 91 PD patients were included in the present study. The demographics and clinical data of both baseline and follow-up evaluation are listed in table 1. Due to the observational design of the study, patients were on a variable drugs regimen: 32 patients were on a single drug class monotherapy (14 on DA, 10 on L-Dopa, eight on IMAO); 52 patients were taking two drugs (23 DA+IMAO; 17 DA+L-Dopa; 12 L-Dopa+IMAO); and seven patients were taking DA+L-Dopa+IMAO.

At baseline, 89 patients (97.8%) referred at least one NMS; at follow-up evaluation, all patients but four (95.6%) referred at least one NMS. Percentage change of each NMS between baseline and follow-up is shown in table 2. 'Anxiety' and 'Sad, blue' were significantly less frequent at follow-up (respectively, p=0.038 and p=0.001), while 'Sex difficulties' (p=0.039), 'Pain' (p=0.028) and 'Weight change' (p=0.004) were more frequently reported.

Both 'Concentrating' and 'Sad, blue' were negatively correlated to use of DA (respectively, Spearman's ρ: −0.258; p=0.01 and Spearman's ρ: −0.357; p=0.02); 'Weight change' was correlated to use of DA (Spearman's ρ: 0.334; p=0.04), to DA-duration (Spearman's ρ: 0.405; p=0.0001) and to DA-LEDD (Spearman's ρ: 0.236 p=0.02). The regression model showed a negative correlation between use of DA and 'Sad, blue' (OR=0.677, p=0.001), after controlling for such confounder factors as use of L-Dopa, IMAO and Total-LEDD. Moreover, positive significant correlations between 'Weight change' and use of DA (OR=18.3; p=0.007) and DA-LEDD (OR=1.1; p=0.03) were found, after controlling for the same confounder factors. The Hosmer—Lemeshow goodness-of-fit test supported our regression model as being valid.

DISCUSSION

To our knowledge, this is the first study to prospectively assess NMS in newly diagnosed PD patients before and after starting dopaminergic therapy. We found that at enrolment, nearly all patients (97.8%) reported at least one NMS, with symptoms belonging to neuropsychiatric and sleep domains being the most frequent. This percentage was found to be quite stable over time (95.6%). Moreover, the number of NMS per patient did not significantly change between baseline and follow-up (5.1±3.8 vs 4.4±2.8), and it was similar among subgroups with or without L-Dopa (data not shown). The results suggest that dopamine replacement seems not to have a dramatic effect on NMS, as that which is seen for motor impairment. Regarding motor disability, it has been previously reported that UPDRS-III progresses with an average of 5.2—8.7 points for 1 year, in the early stage of PD.[19] Due to study design, it is difficult to compare in our group the level of motor disability between the baseline and the follow-up: in fact, the UPDRS III score measured at enrolment reflects an off-medication state, while the score obtained

Table 1 Demographic and clinical data in our group

	Baseline	follow-up
Sex (Male/female)	59/38	59/38
Age (years)	57.6±8.5	61.2±8.3
Disease duration (months)	13.7±5.8	38.4±6.1
UPDRS-III	16.2±7.4	13.3±7.1
Number of NMS per patient	5.1±3.8	4.4±2.8
Total LEDD (mg/day)	—	356.4±169.4
DA (yes/no)	—	61/30
DA-LEDD (mg/day)	—	232.4±97.8
DA duration (months)	—	19.9±3.5
L-Dopa (yes/no)	—	46/45
L-Dopa dosage (mg/day)	—	274.5±138.2
L-Dopa duration (months)	—	14.2±7.8
IMAO (yes/no)	—	50/41
IMAO-LEDD (mg/day)	—	100±0
IMAO duration (months)	—	20.7±2.3

DA, dopamine agonists; DA-LEDD, dopamine agonists-L-Dopa-equivalent daily dosage; IMAO, mono-amino-oxidase inhibitors type-B; IMAO-LEDD, mono-amino-oxidase inhibitors type-B L-Dopa-equivalent daily dosage; LEDD, L-Dopa-equivalent daily dosage; NMS, non-motor symptoms; UPDRS-III, Unified Parkinson's Disease Rating Scale, motor subscore.

Table 2 Frequencies and percentage change of non-motor symptoms

NMS	% Baseline	% Follow-up	Percentage change	p Value
Dribbling	18.7	13.2	−29.4	0.311
Taste/smelling	25.3	23.8	−5.9	0.653
Swallowing	10.9	12.1	+11	0.764
Vomiting	2.2	3.3	+50	0.983
Constipation	9.9	18.7	+88.8	0.092
Bowel incontinence	0	0	NA	–
Bowel emptying incompl.	12.1	10.9	−9.9	0.671
Urgency	17.6	18.7	+6.2	0.852
Nocturia	16.5	7.7	−53.3	0.065
Forgetfulness, memory	16.5	20.1	+2.2	0.454
Loss of interest	27.5	18.7	−5.8	0.167
Concentrating	14.3	18.9	+32.1	0.431
Hallucinations	1.1	3.3	+200	0.623
Delusions	0	2.2	NA	0.494
Sad, blues	43.9	21.1	−51.9	0.001
Anxiety	54.9	39.5	−28.1	0.038
Sex drive	0	3.3	NA	0.25
Sex, difficulty	6.6	17.6	+166.6	0.039
Dizzy	10.9	6.6	−39.4	0.294
Falling	0	0	NA	–
Daytime sleepiness	3.3	4.4	+33.3	0.943
Insomnia	23.1	24.2	+4.7	0.861
Intense, vivid dreams	6.6	9.9	+50	0.419
Acting out during dreams	32.9	37.8	+14.8	0.498
Restless legs	3.3	2.2	−33.3	0.876
Pains	7.7	18.7	+142.8	0.028
Weight	7.7	23.1	+200	0.004
Swelling	14.3	13.2	−0.9	0.831
Sweating	4.4	3.3	−25	0.987
Diplopia	4.4	9.9	+125	0.246

from the follow-up evaluation reflects an on-medication state. However, the relatively small difference between the UPDRS-III values at baseline and follow-up in our group can be easily explained as the result of both the natural progression of motor disability and the improvement given by the dopaminergic therapy. While medications have been found to improve motor performance in all patients, prevalence of NMS changed at follow-up pursuing different patterns, further arguing against a straightforward relationship between dopamine replacement therapy and NMS improvement.

Regarding NMS, the results of our study suggest a non-linear progression: neuropsychiatric symptoms, like depression and anxiety, that were highly prevalent at baseline, showed a significant percentage reduction (respectively, −51.9% and −28.1%) at follow-up. Conversely, 'Sex difficulties', 'Pain' and 'Weight change' became significantly more prevalent, with percentage increases up to 200%. However, the percentage change of these NMS were not completely associated with the dopaminergic replacement. In fact, regarding neuropsychiatric NMS, the results of both correlations and regression analyses suggest that both use of DA and DA-LEDD were associated with the improvement in 'Concentrating' and 'Sad, blue', also after controlling for such confounder factors as demographical data, use of L-Dopa, with IMAO- and total-LEDD. This correlation is in line with many previous studies attempting to use DA for the treatment of depression in PD.[20 21] DA have been suggested to have a specific antidepressant effect, that might be related to limbic dopamine D3 receptors agonism.[22] Regarding the item 'Concentrating', it could have many aspects that might be related both to attention and cognitive functioning. These non-motor features have been suggested to be mediated, at least in part, by disruption of dopaminergic networks.[23–25] Moreover, these NMS have been reported to be improved by use of dopamine agonists.[25 26] In this regard, it should be noticed that we have excluded from the analyses three patients diagnosed as PD-dementia, thus possibly underestimating prevalence of such NMS as depression, apathy, hallucinations and sleep disorders, that have been found to be highly associated with cognitive impairment in PD.[2 11] This option relies mainly on two reason: first, as per protocol, at follow-up examination, we excluded all patients having atypical features, according to UK Brain Bank criteria for PD (ie, we excluded patients showing 'early severe dementia with disturbances of memory, language and praxis')[17]; second, due to the short follow-up, we could not be sure as to how to deal with patients with PD further complicated by dementia rather than with patients having 'other-than-PD' conditions, that can look like idiopathic PD in the earliest stage.

While improving depression and concentration, our results also showed a significant worsening of such NMS as 'Sex difficulties', 'Pain' and 'Weight change'. However, the regression analyses failed to correlate 'Sex difficulties' and 'Pain' with dopaminergic replacement.

Sexual dysfunction in PD may be part of autonomic dysfunction in PD, and testosterone deficiency has also been implicated.[27] Our results suggest that sexual dysfunction are very frequent in early PD and tend to progress over time in spite of any dopaminergic therapeutic regimen.

Pain has been reported to be very frequent in a large cohort of PD patients[28]: this study has shown how unexplained pains are a major component of the non-motor symptom complex of PD, dyskinesia- and dystonia-related pains accounting for a relatively small percentage. Additionally, pain in PD might present as 'central pain'.[29] In our study, proportion of 'Pain' flagged up at follow-up was not related to motor complications. This was an expected finding, due to short disease duration (38.4±6.1 months) in our cohort. Dopamine can modulate pain at several levels within the nervous system, including the thalamus, basal ganglia and cingulate cortex.[9] Moreover, it has been suggested that PD patients have higher pain-induced activation in nociceptive pathways, that can be reduced by L-Dopa.[29 30] Our results suggest that pain is a frequent and increasing complaint in PD patients, even in the early stage of disease, and irrespective of dopaminergic therapy. It also should be noted that in our group, due to short disease duration and little motor disability, mean L-Dopa daily dosage was found to be low (274.5±138.2 mg). Thus, we could not check for an association between pain improvement and higher L-Dopa dosage.

Regarding the item 'Weight change' in the NMSQuest, it refers to weight gain or reduction not related to dietary changes. We reviewed all clinical data and questionnaires of the 21 patients reporting 'Weight change' at follow-up. All patients referred a rising appetite and food introduction, thus, the item 'Weight change' could not be completely satisfied. Anyway, this is an interesting finding, due to the close association between 'Weight change' and use of DA, with patients taking DA being 18 times more likely to develop this symptom (OR=18.3; p=0.007). This result is in line with previous studies suggesting a close relationship between DA use and weight gain.[31] One would suppose that in our group, 'Weight change' might to some extent represent a behavioural addiction and overlap 'Compulsive eating'. We did not administer any structured questionnaire to diagnose a behavioural phenomenon belonging to impulse control disorders (ICD) spectrum in PD,[32] even if

relevant ICD were excluded at clinical interview by each supervising physician involved in the study. However, further longitudinal studies assessing the link between DA use and occurrence of ICD in larger samples are needed, due to the clinical and social impact that ICD have.

In conclusion, we report for the first time a prospective assessment of NMS before and after starting therapy in newly diagnosed PD patients: even if NMS are very frequent in early stage, they tend to remain stable during the first 4 years from appearance of motor symptoms, being only few NMS affected by dopaminergic therapy and, specifically, by the use of DA. It should also be stressed that confounder factors, such as age, disease duration and severity were used as covariates in the regression model, never reaching the statistical threshold which associated them with NMS.

We acknowledge that our study has some limitations, such as the lack of normal controls to assess differences in NMS with PD patients. However, the first aim of our study was to prospectively evaluate NMS progression over dopamine replacement therapy introduction in newly diagnosed PD patients. Moreover, for detection of NMS, we used a validated tool in PD, in line with previous studies.[16 33] Finally, we checked the presence/absence of NMS by means of NMSQuest, and we did not rate their severity, thus missing to assess an NMS severity progression. Further longitudinal studies are required to assess both NMS occurrence and severity in larger samples of PD patients, and their correlation to dopaminergic therapy.

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