

Non-motor symptoms in German and Romanian patients with Parkinson's disease and the differences between the two nationalities

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Abstract: Objective: This study was designed to determine which of the domains of non-motor symptoms associated to Parkinson's disease and which non-motor symptoms are more represented in Parkinson's disease and whether there are differences between Romanian patients and German patients. Material and methods: using Non-motor symptom assessment scale for Parkinson's disease, we evaluated 45 patients, 36 admitted in St. Franziskus Hospital, Ahlen, Germany and 9 in Hospital of Neurologie and Psychiatry, Oradea, Romania. Results: The total scores of non-motor symptoms scale did not significantly differ between the two countries, being however slightly higher for the German patients. Conclusion: There are certain differences between the two nationalities regarding mood/cognition, attention/memory and perception/hallucinations domains.

Key Words: non-motor symptoms, Parkinson's disease, Non-motor symptom assessment scale for Parkinson's disease.

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Introduction

Parkinson's disease (PD) is a neurodegenerative disorder. With a prevalence between 65.6 and 12,500/100,000 and a incidence between 5 and 346/100,000 in Europe (von Campenhausen et al 2005), PD is one of the most frequent neurological disorder. In Germany the prevalence of PD ranges between 100 and 200/100,000 with an increase to 1,800/100,000 in over 65 years old patients (Diener et al 2012). According to Antiparkinson Association Romania there are 72,000 treated patients with PD in Romania (www.asociatia-antiparkinson.ro). In a population of 19,942,642 (data of National Institute of Statistics from Romania) (www.insse.ro) this data shows a prevalence of 0.361%. Regarding incidence of PD in Romania there are no recorded data in the literature. Due to increasing life expectancy is expected in the next 25 years a dramatic increase in the prevalence and incidence of PD (Abdullah et al 2014). Women and men are affected about equally (Linder et al 2010) with slightly higher frequency in males: 1.1 - 2.3 (van den Eeden et al 2005; Wright et al 2010; Ma et al 2014). The onset of disease is usually after 40 years with the highest frequency between 50-65 years, with onset during this period from 75% of cases. In the last two decades the trend is that the onset of disease occur in older age (Pezzoli et al 2014).

Ever since its first description, it was observed that besides tremor at rest, rigidity, bradykinesia and postural instability,

symptoms that are characteristic features of this disease, there are other symptoms such as sleep disturbances, constipation, dysarthria, dysphonia, dysphagia, sialorea, urinary incontinence and delirium (Parkinson 1817). More than a century later, PD symptoms were divided into motor symptoms and non-motor symptoms (NMS). The latter remain insufficiently recognized, understood and investigated by the physician and also often remain unreported by the patient (Schrag et al 2000; Chaudhuri & Healy 2006; Chaudhuri et al 2010; Gallagher et al 2010). The NMS have a critical role in the quality of life of patients with PD (Findley et al 2003; Zesiewicz et al 2010; Martinez-Martin et al 2011; Lageman et al 2014) and they are the major cause of morbidity, hospitalization and mortality (Aarsland et al 2000; Muzerengi et al 2006; Weintraub et al 2008; Thippeswamy et al 2014). Some of the NMS such as impaired smell, REM sleep disorders, constipation, depression, cardiac sympathetic denervation, personality change precede motor symptoms even years and decades, which could be used to detect this disease in its early stages or just before the onset of motor symptoms (Chaudhuri et al 2011; Savica et al 2010; Schapira & Tolosa 2010). Also recognizing the NMS preceding motor symptoms in combination with neuroimaging or other biochemical markers in the future could lead to the detection of patients at risk of developing this disease, discovery of effective neuroprotective therapies and early initiation of therapy and the differentiation from other extrapyramidal disorders.

According to different authors, NMS are divided in different domains: autonomic disorders such as cardiovascular symptoms, gastrointestinal, genitourinary, abnormal sweating. Other domains are neuropsychiatric symptoms, sleep disorders, respiratory disorders, sensory disturbances and others: changes in body weight, impaired smell or taste, fatigue, diplopia, etc. (Chaudhuri et al 2009; Aarsland et al 2013; Pfeiffer et al 2013). For individual assessment of NMS such as sleep disorders, disorders of autonomic system, cognitive disorders and depression in PD were designed separate scales that have been validated and are often used. For general assessment of NMS occurring in PD were designed by a multidisciplinary group of experts and also validated two forms: a questionnaire and a scale of NMS (NMSS) (Chaudhuri et al 2007; Chaudhuri & Martinez-Martin 2006). The questionnaire contains 30 questions to answer with yes or no directly by the patient. The scale also includes 30 questions, however, is applied by the physician and assesses both the frequency and severity with which the NMS occurred last month.

Using NMSS, we have proposed in this study to determine which domains of NMS and which NMS are significantly represented in Parkinson's disease and if there are statistically significant differences between patients in Germany and patients in Romania.

Material and methods

The study included 45 patients with diagnosis of idiopathic PD after Brain-Bank criteria of United Kingdom Parkinson's Disease Society. The patients recruited were in all stages (1-5) of modified Hoehn & Yahr classification. The study group consisted of 36 patients admitted to the neurology department of St. Franziskus Hospital in Ahlen, Germany and in 9 patients admitted in Hospital of Neurology and Psychiatry, Oradea, Romania. Exclusion criteria were the existence of other parkinsonian syndromes than idiopathic PD, presence of symptoms evident in relation to anti-Parkinsonian medication or other diseases, a high degree of dementia, depression or other psychiatric illnesses, insufficient knowledge of German (for cases in Germany). For the assessment we used Non-motor symptom assessment scale for Parkinson's disease. This scale was developed and validated for the first time by Chaudhuri et al in 2007. The scale assesses the severity and frequency of NMS occurring in PD in the last month, is relatively easy to apply, it takes about 10-15 minutes and is applied by the physician. The scale contains 30 questions divided into nine domains, each with several symptoms:

- cardiovascular domain:
 - dizziness/weakness on standing from sitting or lying position
 - fall because of fainting or blacking out
- sleep/fatigue domain:
 - daytime sleepiness
 - fatigue or lack of energy
 - insomnia
 - restless legs syndrome
- mood/cognition domain:
 - lost of interest in surroundings
 - lost of interest in new activities
 - feelings of anxiety, nervousness, sadness for no apparent reason
 - sadness, depression

- flat mood
- difficulty in experiencing pleasure from usual activities or lack
- perception/hallucinations domain:
 - visual hallucinations
 - paranoid ideas
 - diplopia
- attention/memory domain:
 - difficulties in maintaining concentration
 - forgetfulness of related things or events
 - forgetfulness of perform certain activities
- gastrointestinal domain:
 - dribble saliva
 - difficulty swallowing
 - constipation
- urinary domain:
 - difficulty holding urine
 - urinary frequency
 - nocturia
- sexual function domain:
 - altered interest in sex
 - problems in having sex
- miscellaneous domain:
 - pain
 - impaired taste or smell
 - change in weight
 - excessive sweating

By each question is marked frequency and severity of the NMS. The frequency is noted from 1 (less than once a week) to 4 (every day or several times a day), and the severity from 0 (none) to 3 (severe). For each NMS is then obtained a score by multiplying the grade from severity with the grade from the frequency. For each domain is a score obtained by adding the scores from every NMS in that domain and there is a total score of the scale by adding the scores from all domains.

The study was conducted with the written consent of hospital management of St. Franziskus Hospital, Ahlen, Germany, respectively with consent of the patients in group in Romania and approved by the Ethical Committee of University of Medicine and Pharmacy Oradea.

The health statistics program used was MedCalc® version 12.5.0.0 (MedCalc® Software, Mariakerke, Belgium). The results of statistical test were represented by probability hypothesis "null" (p), its value below 0.05 shows a statistically significant difference between the groups studied. The continuous variable with asymmetric distribution were represented by median and IC95%, those with normal distribution by mean and standard deviation in brackets. The tests used were Mann-Whitney test, Fisher's exact test and Spearman test.

Results

The group of patients in Germany comprised 36 patients. Of these 14 (38.9%) were female and 22 (61.1%) were male. Patients were aged between 44 and 92 years with a mean age of 78.7 years and a predominance of patients over 70 years (86.12%). In this group of patients we recorded patients in every Hoehn & Yahr stage (1-5), with predominance of stage 3 (12 patients). 5 patients were in stage 1 of the disease, 4 patients in stage 2, 3

patients in stage 2.5. In each of stages 4 and 5 were 6 patients. In table 1 is represented the distribution of German patients by age.

Table 1. Distribution of German patients by age

Age categories	Number of cases	Percent	P
40-50 years	1	2.8	0.0001*
51-60 years	0	0	
61-70 years	4	11.1	
71-80 years	22	61.1	
81-90 years	8	22.2	
> 90 years	1	2.8	

*Fisher's exact test

The group of patients in Romania comprised 9 patients with PD, of which 6 (66.7%) were female and 3 (33.3%) were male. Age limits were between 58 and 78 years with a mean age of 67.4 years. Also by the patients in Romania prevailed patients over 70 years (88.8%). The distribution of Romanian patients by age is shown in table 2. Patients in this group were found in earlier stages of the disease, stages between 1 and 2.5 Hoehn & Yahr, predominantly were stage 1 and 2 (66.7%). In each of stages 1 and 2 were found 3 patients, one patient was in stage 1.5 and two patients in stage 2.5.

Table 2. Distribution of Romanian patients by age

Age categories	Number of cases	Percent	P
50-60 years	1	11.1%	0.3679*
60-70 years	4	44.4%	
70-80 years	4	44.4%	

*Fisher's exact test

All patients, including those from Romania and those from Germany had at least one NMS. Mean total score of the NMSS for the 45 patients was 83.17 (SD: 50.23) with a range between 10 and 214.

As domains of NMS, in this study the highest scores were achieved in domain mood/cognition, urinary and sleep/fatigue. The lowest scores were those from the perception/hallucinations domain. These results are shown in figure 1.

Comparing the frequency of NMS from each domain by all 45 patients we obtained the following results: the most common cardiovascular symptom was dizziness/weakness on standing from sitting/lying position (88.88%); from sleep/fatigue domain the most common symptom was difficulty falling asleep or staying asleep (71.11%) and need to move the legs/restlessness in legs was less frequently (42.22%). From the mood/cognition domain the most common symptom was loss of interest/motivation to start new activities (84.44%) and the less frequently was nervousness, feelings of anxiety, frightened for no apparent reason (37.77%). Diplopia (8.8%) was the rarest symptom from the domain perception/hallucinations and visual hallucinations appeared in 31.11% from cases. In the attention/memory domain, maintaining attention and memory disturbance on related events or already performed were the most common, both with 68.88%. Among gastrointestinal symptoms constipation was the most

frequently NMS (80%). Problems in holding urine (86.66%) and nocturia (82.22%) were the most common urinary symptoms. The two symptoms in the domain of sexual disorders showed no statistically significant difference. From the miscellaneous domain impaired taste/smell was the most frequently (80%) and change in body weight (8.88%) the rarest NMS.

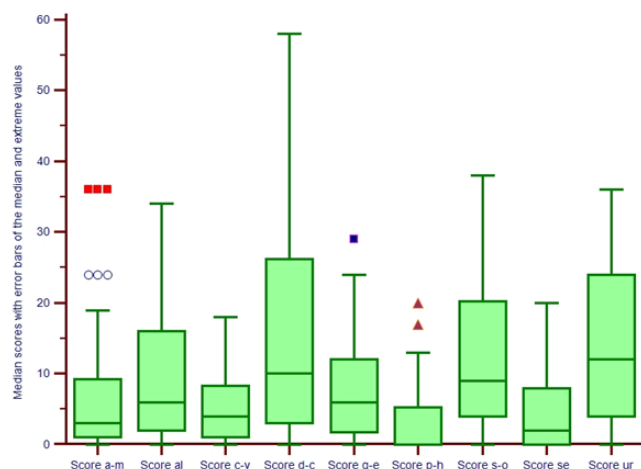


Figure 1. Comparison of NMS domain scores: Score attention/memory (Score a-m), Score miscellaneous (al), Score cardiovascular (c-v), Score mood/cognition (d-c), Score gastrointestinal (g-e), Score perception/hallucinations (p-h), Score sleep/fatigue (s-o), Score sexual function (se), Score urinary (ur)

The female gender had a lower median total score (of 72; CI 95%: 45.3-99.8) as the male gender (83; CI 95%: 50.3-103.8) but the frequency and severity of NMS, represented by total scores of NMSS in this patients sample with PD doesn't differ by gender (p=0.7578, Mann-Whitney test).

Analyzing the differences in scores by gender and by domains of NMS we observed that urinary and gastrointestinal domains are more important in male patients compared to female, the result is represented in figure 2.

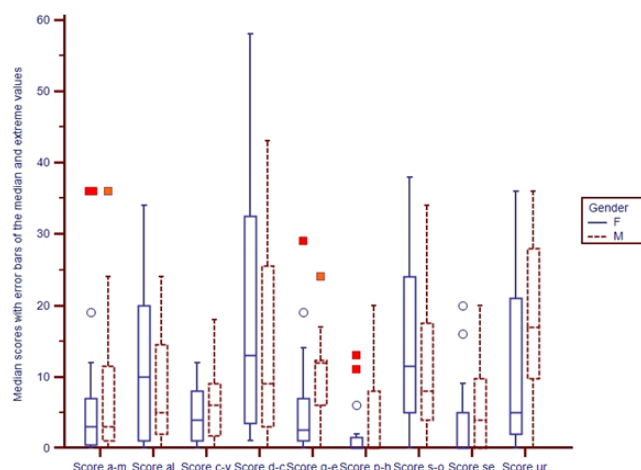


Figure 2. Correlation between median total score on domains of SNM and gender of patients: Score attention/memory (Score a-m), Score miscellaneous (al), Score cardiovascular (c-v), Score mood/cognition (d-c), Score gastrointestinal (g-e), Score perception/hallucinations (p-h), Score sleep/fatigue (s-o), Score sexual function (se), Score urinary (ur).

There is no direct correlation between patient age and severity of NMS: Spearman coefficient = 0.109 (95% CI -0.191 to 0.390), $p = 0.4777$.

Analyzing the correlation between NMS domains and age there is a directly proportional correlation between age and score of the attention/memory domain along with the cardiovascular domain. When comparing total scores for the different stages of PD is observed that patients in stage 5 Hoehn & Yahr showed higher scores of NMS.

In order to check the trend of correlation between stage of the disease, and the total score of NMS, the Spearman test gave the following result: $\rho = 0.489$, CI95%: 0.228 to 0.684, $p = 0.0007$. This means that there is a linear relationship directly proportional between disease stage and NMSS total score.

In table 3 are shown median total scores calculated separately for the two countries.

Table 3. Comparison of median total score of NMS - country of origin

Country	Median total score	CI 95%	P
Germany	81.5	51.6-101.7	0.2067*
Romania	58	29.1-97.3	

*Mann-Whitney test

Frequency and severity of NMS in patients with PD were not significantly different according to the country of origin, yet slightly higher for patients in Germany.

Analyzing the differences in scores for each domain we observed that only mood/cognition domain scores were statistically significantly higher ($p < 0.05$) in patients in Germany. The results are detailed in table 4.

Characteristic for Romanian patients were lower scores of attention/memory domain and perception/hallucinations domain. This can be seen in figure 3.

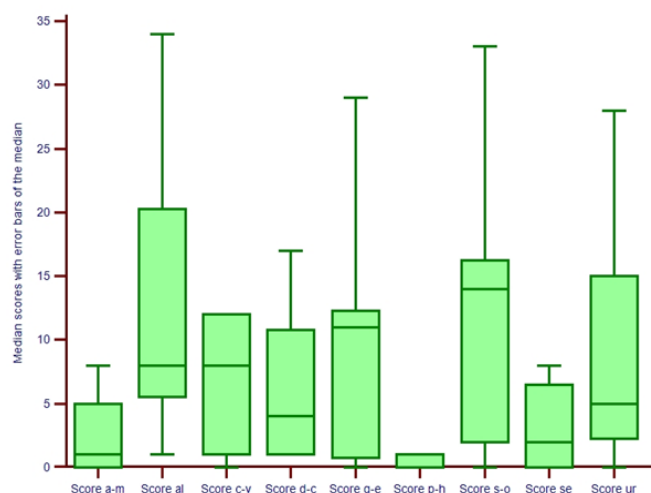


Figure 3. Comparison of NMS domains scores in Romanian patients: Score attention/memory (Score a-m), Score miscellaneous (al), Score cardiovascular (c-v), Score mood/cognition (d-c), Score gastrointestinal (g-e), Score perception/hallucinations (p-h), Score sleep/fatigue (s-o), Score sexual function (se), Score urinary (ur).

Comparing the frequency of each symptom in Romanian patients using mean range and statistical differences through Friedman test we obtained that the most common NMS were dizziness/weakness on standing from sitting or lying position (88.88%), fatigue/lack of energy (88.88%), constipation (77.77%), problems in holding urine (77.77%). By the Romanian patients falls because of fainting or blacking out and visual hallucinations were not present. In the German patients group the most common NMS was loss of interest/motivation to start new activities (91.66%), then dizziness/weakness on standing from sitting or lying position (88.88%) and then nocturia and impairment of taste or smell (both 86.11%). The rarest was change in weight (2.77%) and diplopia (5.55%).

Discussions

In this study we aimed to determine which domains of NMS and which NMS are significantly represented in PD and whether there are statistically significant differences between patients in Germany and patients in Romania.

Regarding the distribution of PD on gender, our findings overlap with those already encountered in literature, a slightly higher frequency in males (Caslake et al 2013).

All patients included in the study had at least one NMS. The frequency of certain NMS differ depending on the tests used for evaluation (questionnaire or scale for NMS). In our study, the highest scores were recorded in the mood/cognition domain, sleep/fatigue and in urinary domain. The lowest scores were obtained in perception/hallucinations domain. Using NMS questionnaire, Cosentino et al in 2013 found the depression as the most frequent, followed by urinary then anxiety/memory. Using also the questionnaire Hwynn (2011) found gastrointestinal symptoms, sleep disturbances and urinary disturbance as the most frequent and using NMS scale: sleep disturbance, gastrointestinal and mood disorders.

The most common symptom of the cardiovascular domain was dizziness/weakness on standing from sitting or lying position. A high frequency of this symptom is encountered also by Sithinamsuwan (2010). From the sleep/fatigue domain the most commonly NMS was difficulty in falling asleep and least frequently need to move the legs/restlessness in legs. From the mood/cognition domain the most common symptom was loss of interest/motivation to start new activities and least frequently was feeling nervous, feelings of anxiety or frighten for no reason. Benito-León (2012) also found a high frequency of apathy. In the perception/hallucinations domain, visual hallucinations and paranoid ideas ranks first place as frequency, results found also by Fénelon (2010), the rarest NMS is diplopia. From attention/memory domain, memory disturbance of related or performed events were the most frequent and disorder of executive memory (patient forgets to do things) the rarest. Using NMS questionnaire, Khoo found in more than half of the patients forgetfulness and poor memory (2013). The most common gastrointestinal symptom is constipation, which supports the results of Sung (2013) and Martinez-Martin (2007). From urinary domain more frequent was nocturia (Martinez-Martin et al 2007) then problems in maintaining urine, unlike Bostantjopoulou which found more frequent urinary urgency and then nocturia (2013). The frequency of the two symptoms in the sexual function domain did not differ statistically significant. From the miscellaneous

Table 4. Comparison of scores for each domain - country of origin

NMS domain scores	Country				P
	Germany		Romania		
	Median	CI 95%	Median	CI 95%	
Attention/memory score	3	2.000 – 9.000	1	0.000 -7.448	0.104
Miscellaneous score	5.5	2.000 -12.000	8	4.276 -20.862	0.164
Cardiovascular score	4	2.000 – 7.000	8	1.000 – 12.000	0.589
Mood/cognition score	16	6.659 – 25.341	4	1.000 – 15.034	0.017
Gastro-intestinal score	6	3.000 – 12.000	11	0.138 – 12.862	0.820
Perception /hallucinations score	0	0.000 – 3.023	0	0.000 – 1.000	0.276
Sleep/fatigue score	8.5	6.659 – 15.023	14	2.000 – 19.310	0.966
Sexual function score	2.5	0.000 – 6.682	2	0.000 – 7.724	0.575
Urinary score	15.5	9.659 – 24.000	5	0.414 – 22.344	0.105

*Mann-Whitney test

domain, the most frequently NMS was altered taste/smell and the least reported changes in body weight. A not very high frequency in weight change is confirmed also by Sheard (2013).

Median total score of NMSS was higher in patients in Germany but the difference was not statistically significant. Analysing the domain scores, we observed that patients in Germany had statistically significantly higher scores on the mood/cognition domain and Romanian patients had statistically significantly lower scores on the attention/memory and perception/hallucinations domains. This is explained by the fact that patients in Romania had a younger age and were found in a less advanced stage as those in Germany, this may be due to the small number of patients included in Romanian group. The most common NMS in Romanian patients were dizziness/weakness on standing from sitting or lying position, fatigue/lack of energy, constipation and problems in maintaining urine in comparison with German patients where the most common NMS was loss of interest/motivation to start new activities, then dizziness/weakness on standing from sitting or lying position and then nocturia and impairment of taste or smell. The rarest NMS in this group was change in weight and diplopia. By the Romanian patients falls because of fainting or blacking out and visual hallucinations were not present.

In our study we found a more significant frequency on a gender in the urinary domain and gastrointestinal domain. They were better represented in males. Other authors found in males more frequent sexual function disorders than in women (Cosentino et al 2013).

Median total score of NMS did not statistically significantly correlated with patients' gender, or age categories (Spearman coefficient), result encountered also in other studies (Chaudhuri et al 2007, Koh et al 2012), but as in other studies (Koh et al 2012, Cosentino et al 2013) in our study there was a significant correlation as a direct proportionality with Hoehn & Yahr stage.

Conclusions

The frequency of certain NMS varies depending on screening method. In literature is observed a higher frequency of questionnaire compared to NMS scale. This is because of the fact that the questionnaire does not require the presence of medical

staff, the answers being given by the patient, which shortens for the physician the time of evaluation. Unlike questionnaire, the NMS scale is applied by the physician. Due to the possibility of clearer explanation of the questions through direct and simultaneous interaction with the physician, using the scale can be more specific than the questionnaire.

Using the NMSS for both Romanian and German patients, certain differences between the two nationalities was observed, namely German patients had statistically significantly higher scores on the mood/cognition domains and Romanian patients had statistically significantly lower scores on the attention/memory and perception/ hallucinations domains.

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