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

Anca-Florina Toma, Petru Mihancea
1 Department of Neurology, St. Franziskus Hospital, Ahlen, Germany; 2 Department of Neurology, Faculty of Medicine and Pharmacy, University of Oradea, Romania.

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.

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, siaorea, 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 (Fridley 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; Muzevengi et al 2006; Wintraub 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
- 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

<table>
<thead>
<tr>
<th>Age categories</th>
<th>Number of cases</th>
<th>Percent</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-50 years</td>
<td>1</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>51-60 years</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>61-70 years</td>
<td>4</td>
<td>11.1</td>
<td>0.0001*</td>
</tr>
<tr>
<td>71-80 years</td>
<td>22</td>
<td>61.1</td>
<td></td>
</tr>
<tr>
<td>81-90 years</td>
<td>8</td>
<td>22.2</td>
<td></td>
</tr>
<tr>
<td>&gt; 90 years</td>
<td>1</td>
<td>2.8</td>
<td></td>
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</table>

*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

<table>
<thead>
<tr>
<th>Age categories</th>
<th>Number of cases</th>
<th>Percent</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-60 years</td>
<td>1</td>
<td>11.1%</td>
<td>0.3679*</td>
</tr>
<tr>
<td>60-70 years</td>
<td>4</td>
<td>44.4%</td>
<td></td>
</tr>
<tr>
<td>70-80 years</td>
<td>4</td>
<td>44.4%</td>
<td></td>
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</table>

*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/weakeness on standing
from sitting/lying position (88.88%); from sleep/fatigue domain
the most common symptom was difficulty falling asleep or stay-
ing 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/motiva-
tion 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 cardio-
vascular (c-v), Score mood/cognition (d-c), Score gastointestinal
(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 gastointestinal (g-e), Score percep-
tion/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

<table>
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<tr>
<th>Country</th>
<th>Median total score</th>
<th>CI 95%</th>
<th>P</th>
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<tr>
<td>Germany</td>
<td>81.5</td>
<td>51.6-101.7</td>
<td>0.2067*</td>
</tr>
<tr>
<td>Romania</td>
<td>58</td>
<td>29.1-97.3</td>
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</table>

*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.

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 blanking 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 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 Bostantjopouloiu 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
that the questionnaire does not require the presence of medical
treatment and can be used independently by the patient. In literature is observed a higher frequency of questions related to psychosocial factors, daily living activities, and physical health, which is consistent with previous studies (Koh et al. 2012, Caslake R, Taylor K, Scott N, Gordon J, Harris C, et al. Age-, gender-,

Conclusions

The frequency of certain NMS varies depending on the age category. In literature is observed a higher frequency of questions related to psychosocial factors, daily living activities, and physical health, which is consistent with previous studies (Koh et al. 2012, Caslake R, Taylor K, Scott N, Gordon J, Harris C, et al. Age-, gender-,

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Authors

• Anca-Florina Toma, Department of Neurology, St. Franziskus Hospital, 55th Robert-Koch-Street, 59227 Ahlen, Germany, email: ancatoma2005@yahoo.com

• Petru Mihancea, Department of Neurology, Faculty of Medicine and Pharmacy, University of Oradea, 1st Universității Street, 410087, Oradea, Romania, EU, email: petru.mihancea@yahoo.com
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