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ORIGINAL ARTICLE

# Relationship between the type and side of motor symptoms with the prevalence of non-motor symptoms in Parkinson's disease

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**KEYWORDS**
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**Abstract**
*Introduction:* The relationship between laterality and asymmetry of Parkinson's disease and non-motor dysfunction has been studied mainly from the perspective of cognitive functions, and the few studies that have included other symptoms have mixed reports. The relationship between non-motor symptoms and the type of onset of the disease has not been studied in detail.
*Objective:* To analyse the association between the side and type of motor onset and the prevalence of non-motor symptoms.
*Patients and methods:* We included 232 patients diagnosed with Parkinson's disease. Type of onset and the side initially affected were documented. The presence of non-motor symptoms was determined by applying the non-motor symptom questionnaire (NMSQuest).
*Results:* When analysing the side of onset and presence of each non-motor symptom explored, statistically significant differences were found in the frequency of hallucinations ($P=.04$) and sleep behaviour disorder ($P<.01$) in subjects with right side onset. The motor type of onset differences were not statistically significant.
*Conclusions:* Subjects with right side onset seem to have a higher risk of having hallucinations and sleep behaviour disorders. These symptoms should be intentionally sought in order to provide treatment and improve the patient's quality of life.


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**PALABRAS CLAVE**
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Lateralidad;
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Rigidez;
Temblor

**Relación entre el tipo y lado de inicio de la sintomatología motora con la frecuencia de síntomas no motores en la enfermedad de Parkinson**

**Resumen**
*Introducción:* La relación de la lateralidad y asimetría de la enfermedad de Parkinson con la sintomatología de disfunción no motora ha sido abordada principalmente desde el punto de vista de las funciones cognitivas, y los escasos estudios que han involucrado otros síntomas han sido contradictorios. La asociación de los síntomas no motores con el tipo de inicio de la enfermedad no ha sido estudiada profundamente.
*Objetivo:* Analizar la asociación entre el lado de inicio de la sintomatología motora, así como del tipo de inicio termorígeno y rígido-bradicinético y la prevalencia de síntomas no motores.
*Pacientes y métodos:* Se incluyeron 232 pacientes con diagnóstico de enfermedad de Parkinson. Se documentó el tipo de inicio y el hemicuerpo afectado inicialmente. La presencia de síntomas no motores se determinó mediante la aplicación del cuestionario de síntomas no motores (NMSQuest).
*Resultados:* Al analizar el lado de inicio y la presencia de los síntomas no motores explorados se encontraron diferencias estadísticamente significativas en la frecuencia de alucinaciones ($p = 0,04$) y del trastorno conductual del sueño ($p < 0,01$) en los sujetos de inicio del lado derecho. En el caso del tipo de inicio no se encontraron diferencias con significación estadística.
*Conclusiones:* Los sujetos con inicio en el hemicuerpo derecho parecen tener un mayor riesgo de presentar tanto alucinaciones como trastorno conductual del sueño. El médico tratante debe buscar de forma intencionada estos síntomas en estos pacientes, y de esta manera otorgar un tratamiento adecuado que impacte en la calidad de vida de los mismos.


## Introduction

The onset of motor symptoms in Parkinson's disease (PD), is generally unilateral, which can be explained histopathologically by a asymmetric nigrostriatal degeneration.[1,2] It has been reported that between 46% to 85% of subjects with PD show asymmetric presentation, with the most frequent being right-side onset.[3] When we look at severity, there is a discrete tendency for it to relate to the patient's dominant side;[4] however, this dominance does not appear to have any effect on the asymmetry of the onset of the disease.[5] Patients with right-hand laterality and right-side motor onset symptoms presented asymmetric persistence more frequently during their disease.[6]

The relationship between non-motor symptoms and the side and onset type of motor symptoms of PD has been dealt with mainly from a cognitive viewpoint and only recently has the association between motor asymmetry and the presence of other non-motor systems been studied.[7] However, the relationship between symptom onset side and motor symptom onset type has not been assessed.

This study was aimed at analysing the association between the onset side of motor symptoms, as well as the onset type (tremor or rigidity/bradykinesia) and the prevalence of non-motor symptoms in Mexican patients with Parkinson's disease.

## Patients and methods

A transversal study was undertaken, including 232 consecutive patients diagnosed with PD according to the UK Brain Bank criteria[8] and a Mini-mental score equal to or greater than 25. All the subjects were seen at the Abnormal Movements Clinic of the National Neurology and Neurosurgery Institute of Mexico City. The demographic variables recorded included gender, age in years and laterality. The clinical variables analysed included age at diagnosis and/or onset of the symptoms, duration of the disease, levodopa equivalent dose (LED) and stage of the disease according to the Hoehn and Yahr (HY)[9] classification.

The onset type was recorded (tremor origin or rigidity/bradykinesia), as well as the side of the body affected initially, through a questionnaire directed at the patient and family. In this study we considered the onset side as the side of the body or limb where the motor symptoms started, and made no reference to the permanence or seriousness of the asymmetry during the evolution of the disease. The previous information was corroborated through a review of the clinical report.

The presence of non-motor symptoms was determined by applying a questionnaire on non-motor symptoms (NMSQuest),[10] which had already been validated for the Mexican population.[11] The NMSQuest is a self-administered screening questionnaire with a total of 30 questions dealing

**Table 1** Demographic characteristics of the sample

| Demographic characteristic | Summary measurement |
|---|---|
| 232 subjects | 102 females/ 130 males |
| Right-hand laterality | 96.8% |
| Age (years) | 63.3±11.3[a] |
| Age when diagnosed (years) | 57±12[a] |
| Duration of the disease (years) | 6.6±5.2[a] |
| Hoehn-Yahr Stage | 2.5 (range: 1-4)[b] |
| Receiving dopamine agonist | 52.2% |
| Receiving levodopa | 67.7% |

[a]Mean±standard deviation.
[b]Median.

with 9 areas and with dichotomous responses of the "yes/no" type. The areas included were digestive, urinary, apathy-attention-memory, hallucinations-delirium, depression-anxiety-anhedonia, sexual, cardiovascular, sleep and miscellaneous. The total test score was obtained from the sum of the affirmative replies. The frequency of affirmative responses by area expressed as a percentage of positive responses over the total maximum was also obtained.

All participants gave their informed consent. The study was approved by the local research committee as well as the ethics committee.

### Statistical analysis

A univariate analysis was carried out to assess the quality of the data collected and the descriptive statistics. A comparative bivariate analysis was carried out using t-test, Mann-Whitney and Chi-squared tests as appropriate. The comparison between the groups was carried out using a variance analysis. A logistical regression analysis was carried out using the presence of individual-non motor symptoms as an outcome variable. A value of $P<.05$ was considered statistically significant. The Statistical Package for the Social Sciences (SPSS) v.11 programme was used for the analysis.

## Results

The demographic characteristics of the population studied are shown in table 1. A percentage of 47.4% (n=110) was classified as having slight disease (HY 1 to 2), 46.6% (n=108) as moderate (HY 2.5 to 3) and only 6% as severe. The percentage of affirmative replies (prevalence) of the non-motor symptoms examined according to side and onset type are shown in table 2.

### Analysis according to onset type

There were 171 subjects (73.7%) who had an onset that started with a tremor and 61 (26.3%) had rigidity-bradykinesia onset. There were no differences found between these 2 groups with respect to gender, severity of the disease, LED and time for evolution; however, there were differences in age, with the tremor group being the greatest (64.5±11 vs 60±11.2 years; $P=.01$).

When comparing the onset type with the percentage of positive responses in each NMSQuest area, we found an association at the statistical significance limit ($P=.05$) between tremor origin onset and the hallucinations/ delirium area. When the onset type and the presence of each of the non-motor symptoms examined were analysed, we found that dysphagia was more common in cases that started with rigidity/ bradykinesia symptoms ($P=.04$), while hallucinations were more common in subjects with a tremor origin onset ($P=.01$). The rest of the symptoms had no statistically significant differences.

### Analysis according to onset side

There were onset manifestations of the right side in 59.5% (n=138) of cases, while the remaining 40.5% had left-side onset. There were no differences regarding distribution according to gender, LED, time of evolution and HY stage when comparing the right side or left side onset groups. The subjects that had right onset were older (65.3±10.6 vs 60.3±11.6 years; $P=.001$).

When the relationship between the onset side and the percentage of positive responses in each area was analysed, we did not find statistically significant associations. When analysing the onset side and the presence of each of the non-motor symptoms examined, we found there was a greater frequency of urinary urgency in patients with left-side onset ($P=.01$). Hallucinations and sleep behaviour disorders were more common in subjects with right-side onset ($P=.04$ and $P<.01$; respectively).

### Analysis according to type and onset

Altogether there were 106 subjects with right-side tremor onset (45.7%), 63 with left-side tremor onset (27.2%), 33 with right-side rigidity/ bradykinesia onset and 30 with left-side rigidity/ bradykinesia onset (14.2 and 12.9% respectively). Table 3 shows the comparison between these groups.

The variance analysis dividing the subjects into 4 groups (right-side tremor origin, left-side tremor origin, right-side rigidity/ bradykinesia onset and left-side rigidity/ bradykinesia onset) did not show any differences between these groups and percentage of positive responses by area. The score by area for each group is shown in table 4.

When these same groups were analysed individually for the presence of each non-motor symptom, we found a greater frequency for the items that examined urinary urgency in subjects with left-side rigidity/ bradykinesia onset ($P=.03$), while hallucinations were more common in subjects with right-side tremor onset ($P=.02$). Sleep behaviour disorders with rapid eye movements were most common in subjects with right-side rigidity/ bradykinesia onset ($P=.03$).

The logistic regression model that took the presence of each non-motor symptom as a variable showed implication of the onset side and type only when it referred to hallucinations and sleep behaviour disorders. In the case of

**Table 2** Percentage of affirmative replies by NMSQuest item according to side and onset type

| Item | Onset side: | | | Onset type | | |
|---|---|---|---|---|---|---|
| | Right (n=107) | Left (n=94) | P[a] | Tremor (n=171) | Rigidity (n=61) | P[a] |
| Dribbling | 22.4 | 29.7 | 0.20 | 23.3 | 31.1 | 0.23 |
| Loss of taste/ smell | 31.1 | 37.2 | 0.33 | 35.6 | 27.8 | 0.26 |
| Difficulty in swallowing | 29.7 | 39.5 | 0.17 | 29.2 | 44.2 | 0.04 |
| Vomiting/ nausea | 15.9 | 22.3 | 0.21 | 19.2 | 16.3 | 0.62 |
| Constipation | 59.4 | 55.3 | 0.37 | 57.8 | 57.3 | 0.24 |
| Faecal incontinence | 8.6 | 11.7 | 0.45 | 9.3 | 11.4 | 0.64 |
| Incomplete bowel emptying | 40.5 | 34 | 0.31 | 35.6 | 44.2 | 0.24 |
| Urinary urgency | 52.2 | 70.2 | 0.01 | 57.3 | 65.5 | 0.26 |
| Nocturia | 63.7 | 59.5 | 0.52 | 61.9 | 62.2 | 0.97 |
| Unexplained pain | 41.3 | 42.5 | 0.85 | 42.1 | 40.9 | 0.88 |
| Change in weight | 25.3 | 30.9 | 0.36 | 26.9 | 29.5 | 0.70 |
| Memory | 52.2 | 40.4 | 0.08 | 47.3 | 47.5 | 0.98 |
| Apathy | 32.6 | 35.1 | 0.69 | 32.1 | 37.7 | 0.43 |
| Hallucinations | 23.1 | 12.7 | 0.04 | 22.8 | 8.1 | 0.01 |
| Problems of concentration | 41.3 | 36.1 | 0.43 | 38.5 | 40.9 | 0.74 |
| Sadness | 71 | 60.6 | 0.09 | 65.4 | 70.5 | 0.48 |
| Anxiety | 42.7 | 47.8 | 0.44 | 44.4 | 45.9 | 0.84 |
| Change in libido | 34 | 40.4 | 0.32 | 35.6 | 39.3 | 0.61 |
| Sexual difficulties | 35.5 | 39.3 | 0.55 | 34.5 | 44.2 | 0.18 |
| Dizziness | 45.6 | 45.7 | 0.98 | 45 | 47.5 | 0.74 |
| Falls | 37.6 | 32.9 | 0.46 | 33.9 | 40.9 | 0.32 |
| Daytime sleepiness | 23.9 | 35.1 | 0.06 | 28.9 | 27.8 | 0.91 |
| Insomnia | 42 | 55.3 | 0.05 | 48.5 | 44.2 | 0.57 |
| Vivid dreams | 41.3 | 32.9 | 0.20 | 38 | 37.7 | 0.97 |
| Sleep behaviour disorders | 40.5 | 22.3 | <0.01 | 34.5 | 29.5 | 0.48 |
| Restless Legs | 47.8 | 44.6 | 0.64 | 43.8 | 54.1 | 0.17 |
| Oedema | 23.9 | 23.4 | 0.93 | 22.8 | 26.2 | 0.59 |
| Excessive sweating | 36.9 | 42.5 | 0.39 | 38 | 42.6 | 0.53 |
| Diplopia | 21 | 12.7 | 0.11 | 19.3 | 13.1 | 0.28 |
| Delirium | 11.6 | 8.5 | 0.30 | 9.9 | 9.8 | 0.98 |

[a]Chi-square test; statistical significance $P<.05$.

hallucinations, the predictor factors were right-side onset ($P=.01$), levodopa equivalent doses ($P=.02$), Hoehn and Yahr Stage ($P=.04$) and age ($P<.01$). In sleep behaviour disorders, the determinants were LED ($P=.04$) and right-side onset ($P=.005$). There was no other significant effect for gender or onset type of the motor symptoms.

## Discussion

The relationship between laterality and asymmetry of PD and non-motor dysfunction has mainly been studied from a cognitive function point of view. We observed that right-side onset subjects present a decrease in creative verbal

**Table 3** Characteristics of the sample by onset type and side

| | Right-hand tremor (n=106) | Left-hand tremor (n=63) | Right-hand rigidity (n=33) | Left-hand rigidity (n=30) | P[a] |
|---|---|---|---|---|---|
| Age (years)[a] | 66.3±9.9 | 61.1±11.9 | 62.1±12.2 | 58.6±11.3 | 0.001 |
| Females (%) | 49 | 43 | 36 | 37 | 0.46 |
| Duration of the disease (years)[a] | 6.5±5.6 | 6.3±4.2 | 7.9±5.8 | 6.3±5.7 | 0.52 |
| Hoehn-Yahr Stage[a] | 2.2 | 2.5 | 2.5 | 2.3 | 0.06 |
| LEDD (mg) | 503.1±405.3 | 506.5±395 | 559±440.6 | 508±484.6 | 0.92 |

LEDD: Levodopa equivalent daily dose.
[a]Mean±standard deviation; statistical significance $P<.05$.

**Table 4** Mean comparison of the NMSQuest scores in areas according to group type and onset of Parkinson's disease

| Area | Right-hand tremor (n=106) | Left-hand tremor (n=63) | Right-hand rigidity (n=33) | Left-hand rigidity (n=30) | $P^a$ |
|---|---|---|---|---|---|
| Digestive | 2.1±1.6 | 2.2±1.8 | 2.0±1.5 | 2.8±2.4 | 0.22 |
| Urinary | 1.1±0.8 | 1.3±0.7 | 1.2±0.8 | 1.3±0.7 | 0.45 |
| Apathy/attention, memory | 1.3±1.0 | 1±1.1 | 1.1±1 | 1.4±1 | 0.21 |
| Hallucinations/delirium | 0.4±0.7 | 0.2±0.5 | 0.2±0.5 | 0.1±0.4 | 0.10 |
| Depression/anxiety | 1.2±0.8 | 1±0.9 | 1±0.8 | 1.3±0.8 | 0.23 |
| Sexual | 0.7±0.8 | 0.8±0.8 | 0.7±0.8 | 0.9±0.9 | 0.65 |
| Cardiovascular | 0.7±0.7 | 0.7±0.7 | 0.8±0.7 | 0.7±0.7 | 0.90 |
| Sleep | 1.9±1.5 | 1.9±1.5 | 2±1.3 | 1.9±1.4 | 0.98 |
| Miscellaneous | 1.6±1.3 | 1.7±1.2 | 1.6±1.3 | 1.6±1.4 | 0.99 |
| NMSQuest total | 10.9±6 | 10.8±5.8 | 10.6±5.7 | 12.1±4.9 | 0.71 |

[a]Variance analysis of a factor; statistical significance $P<.05$.

fluency,[12] as well as changes in verbal memory and visual perceptual skills.[13] Proton emission tomography studies revealed that spatial tasks require the integrity of the right striate (left-side motor), while the executive verbal tasks depend on the left side (right motor).[14] Right-side motor symptoms have generally been associated with a lower score in the Mini-mental and DRS-2 (Dementia Rating Scale);[15] however, we also saw that subjects with right-side tremor onset PD develop better that those with left-side or right-side onset of the rigidity/bradykinesia type.[16] On the other hand, left-side motor dysfunction has been associated with poor spatial and visual memory.[17,18]

We did not find an association between the onset side or type and our rate of positive responses in the memory area in our study. However, because the non-motor symptom instrument is self-administered, we deliberately excluded patients who had a Mini-mental score of 24 or less. This limits the interpretation of the results with respect to cognitive function.

We have suggested that the presence of depression is determined by a greater affectation on the dominant side, more than the asymmetry of the disease.[19] Given that 97% of patients included had right-side dominance, there is a clear over-representation in this group, which does not allow for conjectures regarding the effect of the dominant side. Even so, we did not find a difference in the items and areas affected and in the onset side and type.

Cubo et al, in their study of motor manifestations, reported that subjects with a right-side motor manifestation presented a higher psychosis instrument score in PD, suggesting a greater implication of the left hemisphere.[7] Contradicting this, Stavitsky et al reported that patients with PD affecting the left side presented a greater frequency of nocturnal hallucinations, daytime sleepiness and vivid dreams than those with right-side dominance; however, the fact that the sample size in this study was low should be taken into account.[20] In this work, patients with motor onset in the right side had a greater affirmative response for presenting hallucinations, as well as sleep behaviour disorders. It has been suggested that sleep behaviour disorders of rapid eye movements increases the probability of presenting hallucinations, particularly in patients who are of an advanced age and have greater motor alteration.[21] In our sample, the mean age of the subjects with tremor origin and also those with right-side onset was greater than in the others. However, we should mention that when results were controlled for this variable, the effect of the type and side on the hallucinations and on sleep behaviour disorder frequency was maintained with statistical significance.

Left-side onset was related to the presence of urinary urgency. Functional magnetic resonance studies have shown that the areas involved in the control of urination include the supplementary motor area, the bilateral putamen, the right parietal cortex, the right side limbic system and the right cerebellum,[22] so the affectation of some of these structures could explain this pattern.

However, the onset type of the subjects that started with a tremor showed a tendency to present a higher rate of positive responses in the hallucinations/delirium area. When the items for the presence of hallucinations were analysed individually, they reached statistical significance for both tremor type and right-side onset. Finally, rigidity/bradykinesia onset was associated only with dysphagia, which was expected, as this symptom is also related to dorsal motor nucleus involvement of the vagus nerve, with oropharyngeal muscle stiffness.

The limitations of this study included the fact that the NMSQuest instrument was designed to record responses of a "yes/no" type and did not include severity or frequency. This fact stops us from measuring the severity of the non-motor symptoms, which is why it would be better to use other scales such as the non-motor symptom scale (NMSS)[23] or specific instruments such as SCOPA (Scales for Outcomes in Parkinson's Disease).[24] This instrument was chosen because it had a proper consistency and validity, it could be self-administered and was simple to reply to, which allowed it to be sent by post or applied in the waiting room. Another point to consider is the fact that laterality was defined as the side or limb the patient indicated as being the onset side and this was corroborated with the information of the clinical history. All these data are susceptible to a recall bias; their use was selected because the objective to be studied was to assess the onset type and side, not the asymmetry of the disease. It should also be mentioned that

the patients found themselves in a mean HY stage of 2.5 during the assessment time, which meant that the disease was already bilateral.

To conclude, subjects with PD with right-side onset seem to have a greater risk of presenting hallucinations as well as sleep behavioural disorders. That is why doctors should intentionally try and find these disorders and, if applicable, perform a more detailed study using specific clinometric scales as well as polysomnography in the case of sleep behavioural disorders.

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## Conflict of interest

The authors have no conflict of interest to declare.

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