Original article

Handedness and dominant side of symptoms in Parkinson's disease

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A R T I C L E   I N F O

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A B S T R A C T

Background and objective: To investigate the association between handedness and the side of symptom dominance in Parkinson’s disease (PD).

Patients and methods: One hundred and forty-six PD patients with symmetric symptoms (92 males and 54 females), aged 64.3 ± 9.1 years old, from a series of 247 PD patients were assessed for handedness and clinical features. The severity of PD was scored by unified Parkinson’s disease rating scale (UPDRS) and Hoehn-Yahr staging on the “ON” state.

Results: Of 134 right-handed patients (91.8%), 83 (61.7%) had an initial onset on the right side ($P = 0.008$), while of 12 left-handed patients (8.2%), 9 (75.0%) had an initial onset on the left side ($P = 0.013$). Out of right-handed patients, 103 (76.9%) had the right-side dominance of PD symptoms ($P < 0.001$). Among the left-handed subjects, 7 patients (58.3%) had left-sided and 5 patients (41.7%) had right-sided symptom dominance ($P = 0.564$). In general, dominant side of symptoms was in accordance with handedness ($P = 0.008$). In right-handed patients, rest tremor was the most common initial symptom ($P < 0.001$), while rest tremor and rigidity-bradykinesia were initial symptoms in left-handed patients ($P = 0.366$).

Conclusions: PD symptoms emerge more often on the dominant hand-side, and the dominant side of symptoms is in accordance with handedness.

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Dominancia manual y dominancia de los síntomas en la enfermedad de Parkinson

R E S U M E N

Fundamento y objetivo: Investigar la asociación entre la dominancia manual y el lado dominante de los síntomas en la enfermedad de Parkinson (EP).

Pacientes y métodos: Ciento cuarenta y seis pacientes con EP y síntomas simétricos (92 hombres y 54 mujeres), con edades entre 64.3 ± 9.1 años, de entre 247 pacientes con EP, fueron evaluados según si eran diestros o zurdos y la clínica que presentaban. La gravedad de la EP fue determinada por la Unified Parkinson Disease Rating Scale (UPDRS, Escala Unificada para la Evaluación de la Enfermedad de Parkinson) y el estado «ON» de la clasificación de Hoehn-Yahr.

Resultados: De los 134 pacientes diestros (91.8%), 83 (61.7%) presentaron la aparición inicial de síntomas en el lado derecho ($P = 0.008$), mientras que de 12 pacientes zurdos (8.2%), 9 (75.0%) tuvieron la aparición inicial en el lado izquierdo ($p = 0.013$). Entre los pacientes diestros, 103 (76.9%) mostraron un dominio derecho de los síntomas de la enfermedad ($p < 0.001$). Entre los sujetos zurdos, 7 (58.3%) los mostraron en el lado izquierdo y 5 (41.7%) presentaban los síntomas en el lado derecho ($P = 0.564$). En general, el lado dominante de los síntomas se relacionaba con la dominancia manual ($P = 0.008$). En los pacientes diestros, el temblor de reposo fue el síntoma inicial más frecuente ($p < 0.001$), mientras que el temblor de reposo y la rígidez y bradicinesia se presentaron como síntomas iniciales en los pacientes zurdos ($P = 0.366$).

Conclusiones: Los síntomas de la enfermedad aparecen con más frecuencia en el lado de la mano dominante, y el lado dominante de los síntomas se relaciona con la dominancia manual.

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Introduction

Parkinson’s disease (PD) is characterized by symptoms of tremor, rigidity, bradykinesia, and abnormal posture. Unilateral predominance of symptoms and signs is one of the most important diagnostic basis of PD and it is so conspicuous that it serves as a clinical parameter to differentiate it from other neurodegenerative diseases, such as multiple system atrophy, diffuse Lewy body disease, and progressive supranuclear palsy, in which there is usually no side predominance. The asymmetry may continue throughout the span of the disease and the worst symptoms on the side of onset often persist long after the disease becomes clinical.\(^1\) To date, there is no valid explanation for asymmetry in PD. Some studies showed that asymmetry may relate to significant less striatal functional binding,\(^2\) reduced dopamine transporter uptake,\(^3\) and more loss of nigral dopaminergic neurons in the contralateral side to the predominantly affected limbs.\(^4\) It is a well-known lateralized function in normal conditions of hand dominance, which is similar to the heterogeneity of lateralized appearance of PD motor symptoms. It has been speculated that there may be a relationship between handedness and lateralization of PD symptoms, which might provide a clue for a possible explanation of unilateral appearance of PD. Although this issue has been addressed in previous studies in whites,\(^3\)-\(^5\) no similar study has been reported in Chinese Han population to date. Furthermore, the different distribution of handedness in whites\(^5\) and Chinese population\(^1\) might lead to different results. In view of this, the relationship between handedness and lateralization of PD symptoms in Chinese is worthy to study. The aim of this study was to identify a possible association between handedness and the side of symptom dominance of PD in Chinese Han population.

Materials and methods

Study population

PD patients were recruited from the Department of Neurology of First Affiliated Hospital of the Medical College of Xi’an Jiaotong University. Two hundred and forty-seven patients diagnosed of PD met the UK Brain Bank criteria\(^6\) for idiopathic PD diagnosis. We meticulously collected data of all left-handed Chinese Han patients. One hundred and one patients were excluded for reasons such as missing data, unclear medical history, and mixed handedness. A group of 146 subjects were finally included.

Methods

This study was approved by the Ethical Committee of First Affiliated Hospital of Medical College of Xi’an Jiaotong University. Informed consent forms were received from participants before entering this trial. We retrospectively identified 146 PD patients who had complete data of sex, age at diagnosis, handedness, initial motor symptom, and site of initial motor symptom, among others. Disease severity was scored by the unified Parkinson’s disease rating scale (UPDRS) and Hoehn-Yahr staging on the “ON” state. Predominantly affected side was initially assessed by neurological physical examination and self-report from patients and determined by signal side motor score by a neurologist. Signal side motor score is the total score of finger taps, hand movements, rapid alternating movements of hands, and leg agility in UPDRSIII. Scores on the right side or left side were collected separately. The side with higher score is the side having more symptoms.

Handedness was defined as the hand used for better fine movements like writing and using chopsticks according to the distribution of handedness in Chinese population.\(^1\)

Statistical analyses

Nominal data were expressed as frequency and numerical data were expressed as mean ± standard deviation (SD). Statistical analyses were performed with the SPSS statistical software (version 16.0; SPSS Inc., Chicago, IL, USA). Frequency data were compared by chi-square test or Fisher exact test. Numerical data were compared by the Mann–Whitney U test. Kappa identity test was used for the correlation between handedness and dominant side of symptoms. Differences in values were considered significant if \(P < 0.05\). Kappa identity test was performed and correlations were considered if \(P < 0.05\).

Results

There were 146 patients with 92 (63.0%) males and 54 (37.0%) females. A total of 108 patients (74.0%) were characterized by right-sided symptom dominance, while in 38 patients (26.0%) symptoms were dominant on the left side. Handedness was right-sided in 134 patients (91.8%) and left-sided in 12 patients (8.2%).

There was a significant association between handedness and onset side (\(P = 0.008\)). The initial symptoms appeared on the right side in 61.7% of the right-handed patients (\(P = 0.008\)) and on the left side in 75% of the left-handed patients (\(P = 0.013\)). More predominant symptoms were observed on the right side in 76.9% of right-handed patients (\(P < 0.001\)), and on the left side in 53.8% of left-handed patients (\(P = 0.564\)). In all cases, handedness was consistent with the more affected side (\(P = 0.008\)). In right-handed patients, the rest tremor was the most common initial symptom (\(P < 0.001\)), while in left-handed patients rest tremor and rigidity-bradykinesia were observed equally as initial symptoms (\(P = 0.366\)). Initial motor symptom was more common on arms than legs, either in right- or left-handed PD patient (Table 1).

Regardless of the dominant side, out of 88 patients with initial symptoms on the dominant side, 89.8% had these initial symptoms on the right side (\(P < 0.001\)), while in 58 patients who had initial symptoms on the non-dominant side, the initial symptoms were observed on the left side (\(P < 0.001\)). Both subgroups shared some common features. Rest tremor was the most common initial symptom (\(P < 0.001\)), initial motor symptom was more often observed on arms (\(P < 0.001\)), and serious symptoms tended to develop predominantly on the right-side (\(P < 0.001\), Table 2).

Table 1: Relationship between handedness and motor symptoms of PD

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Right-handed patients ((n = 134))</th>
<th>Left-handed patients ((n = 12))</th>
<th>Total patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Side of initial symptoms [n %]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>83 (61.7)</td>
<td>3 (25.0)</td>
<td>86</td>
</tr>
<tr>
<td>Left</td>
<td>51 (38.3)</td>
<td>9 (75.0)</td>
<td>60</td>
</tr>
<tr>
<td><strong>Site of initial symptoms [n %]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arms</td>
<td>87 (65.0)</td>
<td>7 (58.4)</td>
<td>94</td>
</tr>
<tr>
<td>Legs</td>
<td>31 (23.1)</td>
<td>3 (25.0)</td>
<td>34</td>
</tr>
<tr>
<td>Others</td>
<td>16 (11.9)</td>
<td>2 (16.7)</td>
<td>18</td>
</tr>
<tr>
<td><strong>Initial symptoms [n %]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>87 (64.0)</td>
<td>5 (41.7)</td>
<td>92</td>
</tr>
<tr>
<td>Rigidity-bradykinesia</td>
<td>30 (22.4)</td>
<td>7 (58.3)</td>
<td>37</td>
</tr>
<tr>
<td>Others</td>
<td>17 (12.7)</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td><strong>Side of more predominant symptoms [n %]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>103 (76.9)</td>
<td>5 (41.7)</td>
<td>108</td>
</tr>
<tr>
<td>Left</td>
<td>31 (23.1)</td>
<td>7 (58.3)</td>
<td>38</td>
</tr>
</tbody>
</table>
Table 2
Comparison of motor symptoms between initial symptoms on the dominant side and on the non-dominant side.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Initial symptoms on dominant side (n = 88)</th>
<th>Initial symptoms on non-dominant side (n = 58)</th>
<th>Total patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Side of initial symptoms [n (%)]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>79 (88.9)</td>
<td>6 (10.3)</td>
<td>85</td>
</tr>
<tr>
<td>Left</td>
<td>9 (10.2)</td>
<td>52 (89.7)</td>
<td>61</td>
</tr>
<tr>
<td><strong>Site of initial symptoms [n (%)]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arms</td>
<td>60 (68.2)</td>
<td>33 (56.9)</td>
<td>93</td>
</tr>
<tr>
<td>Legs</td>
<td>16 (18.2)</td>
<td>18 (31.0)</td>
<td>34</td>
</tr>
<tr>
<td>Others</td>
<td>12 (13.6)</td>
<td>7 (12.1)</td>
<td>19</td>
</tr>
<tr>
<td><strong>Initial symptoms [n (%)]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>57 (64.8)</td>
<td>35 (60.3)</td>
<td>92</td>
</tr>
<tr>
<td>Rigidity-bradykinesia</td>
<td>20 (22.8)</td>
<td>17 (29.3)</td>
<td>37</td>
</tr>
<tr>
<td>Others</td>
<td>11 (12.5)</td>
<td>6 (10.3)</td>
<td>17</td>
</tr>
<tr>
<td><strong>Side of more predominant symptoms [n (%)]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>64 (72.7)</td>
<td>42 (72.4)</td>
<td>106</td>
</tr>
<tr>
<td>Left</td>
<td>24 (27.3)</td>
<td>16 (27.6)</td>
<td>40</td>
</tr>
</tbody>
</table>

Discussion

As it is known, there is a difference in handedness distribution between whites (10% left-handed in the general population10) and Chinese Han population (2–5% left-handedness in the general population11,12 and 4.8% in this study) due to different genetic backgrounds, cultures, and living habits. All the previous reported studies were carried out in whites, including patients from Europe, USA, and Spain.6,7,9,13 Recently a meta-analysis on this issue was published, which included 10 studies and 4405 asymmetric PD white patients, with no Chinese patients.8 However, the distributions of handedness in whites and Chinese are different, which might cause different results and conclusions. Thus, the relationship between handedness and lateralization of PD symptoms in Chinese should be re-investigated.

This study showed that initial symptoms developed on the dominant side more commonly and handedness was consistent with the more affected side in PD patients, in accordance with previous studies.6,7,9,13 In the right-handed patients, tremor is the most common initial symptom. In contrast, among left-handed patients, tremor and rigidity-bradykinesia have the same probability to develop as an initial symptom. All patients had their first symptoms on arms.

Though some previous studies have implied that there was a relationship between handedness and motor symptoms, it is controversial and difficult to figure out such relationship because of contradictory results,14,15 pointing out that this issue should be investigated further. In fact, our study showed a significant correlation between them. To date, there is no valid explanation why handedness relates with motor symptoms in PD. Some studies have reported that patients experiencing first symptom on the dominant side might reflect the fact that patients notice changes earlier on the side that is most extensively used. However, this cannot explain why an unilateral distribution of symptoms remains during disease progression and the first symptoms correspond with the more affected side.1 It is possible that some anatomical or physiological reasons may explain this uncertainty, other than patients noticing changes earlier on the dominant side.

There is no plausible explanation about the unilateral predominance of the motor symptoms in PD. It has been reported that reduced dopamine transporter uptake3 and more loss of nigral dopaminergic neurons4 occur on the contralateral side to the side with clinical symptoms, which may mean that inconsistency of damage in the substantia nigra induced unilateral symptoms. Whether increased movement complexity, enabled by the most skilled hand, is a risk factor for dopaminergic neuron loss in the dominant hemisphere has to be confirmed. Cohen et al.16 injected 6-hydroxydopamine (6-OHDA) into unilateral striatum and induced dysfunction of the contralateral limbs with preferential use of the ipsilateral limbs. After induction of forced enhancement of contralateral limb movements by casting and immobilizing the ipsilateral limbs, the animals displayed no detectable impairment or asymmetry of limb use, indicating that forced exercise might be protective. In other words, movements at least do not induce loss of dopaminergic neuron and there is no relationship between movement complexity of the dominant side and initial symptoms on the dominant side.

Several mechanisms have tried to explain unilateral motor symptoms in PD. Genetic predisposition leads to greater vulnerability in substantia nigra of one side.17 Environmental, metabolic, toxic factors, inborn variations in the number of dopaminergic neurons,18 and one-sided weakness of the midbrain blood–brain barrier19 also play important roles. Possible pathogenic mechanisms, including oxidative stress, inflammation, excitotoxicity, mitochondrial impairment, and abnormal deposition of misfolded protein aggregates may contribute to the phenomenon. The association between handedness and the side of symptoms dominance imply that studies of handedness and the anatomy and physiology of substantia nigra may add clues to the mechanism.

Conclusion

The current study showed that PD symptoms tend to start on the dominant hand–side, which is in accordance with the dominant side of PD symptoms in PD patients. This finding provides a novel clue for a possible explanation of the onset of PD.

Conflict of interest

The authors declare no conflicts of interest.

References