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ORIGINAL ARTICLE

Pitfalls and caveats in the diagnostic pathway of people with Parkinson's disease

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Abstract

Objective: *We carried out a cross-sectional study to identify the factors involved in each stage of the diagnosis pathway that may lead to a diagnostic delay in persons with Parkinson's disease (PD).* **Materials and Methods:** *Consecutive patients with PD were included. A questionnaire assessing the recognition of the initial symptoms, pathway to seek attention diagnosis and perception on the diagnostic time and identified barriers was applied. Diagnosis delay was defined as ≥ 12 months between initial recognition of the symptom and the definitive diagnosis of PD.* **Results:** *A total of 114 patients (57.9% male) with PD were included in the study. The overall median time of the diagnosis pathway was 14.5 (interquartile range [IQR] 31) months and the longest time in this pathway was between the first medical consultation and the definitive diagnosis of PD, a median of 9 (IQR 14) months. The main appraisal of the first symptom was being "not worried" (48.2%). The mains reasons for seeking medical attention were symptom worsening (42.1%). Patient's perception on the diagnostic time was reported as very adequate/adequate in 52.7%. Barriers delaying the diagnosis identified included the belief of spontaneous symptoms relief and lack of trust in their doctor.* **Conclusion:** *Both the person with PD and the physician play a shared role in the diagnosis of PD. Improving the awareness of the disease, as well as improving medical education on PD, could result in a timely diagnosis.*

Keywords: *Parkinson's disease. Delayed diagnosis. Diagnosis pathway. Primary health care. Diagnosis.*

Escollos y salvedades en la vía de diagnóstico de las personas con enfermedad de Parkinson

Resumen

Objetivo. *Se llevó a cabo un estudio transversal para identificar los factores involucrados en cada etapa del camino diagnóstica que pueden conducir a un retraso diagnóstico en personas con enfermedad de Parkinson (EP).* **Material y métodos**. *Se incluyeron pacientes consecutivos con EP. Se aplicó un cuestionario que evaluó el reconocimiento de los síntomas iniciales, la vía para buscar el diagnóstico de atención y la percepción sobre el tiempo de diagnóstico y las barreras identificadas. El retraso en el diagnóstico se definió como ≥12 meses entre el reconocimiento inicial del síntoma y el diagnóstico definitivo de EP.* **Resultados.** *Se incluyeron a 114 pacientes (57.9% hombres) con EP. El tiempo medio del diagnóstico fue de 14.5 (RIC 31) meses y el tiempo más largo en este proceso fue entre la primera consulta médica y el*

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diagnóstico definitivo de EP con una mediana de 9 (RIC 14) meses. La principal percepción del primer síntoma fue estar "no preocupado" (48.2%). Los principales motivos de consulta médica fueron el agravamiento de los síntomas (42.1%). La percepción del paciente sobre el tiempo de diagnóstico se informó como muy adecuada/adecuada en el 52.7%. Las barreras que retrasaron el diagnóstico identificadas incluyeron la creencia de una mejoría espontáneo de los síntomas y la falta de confianza en su médico. **Conclusiones**. *Tanto la persona con EP como el médico juegan un papel compartido en el diagnóstico de EP. Mejorar la conciencia sobre la enfermedad, así como mejorar la educación médica sobre la EP, podría resultar en un diagnóstico oportuno.*

Palabras clave: *Enfermedad de Parkinson. Diagnóstico tardío. Camino diagnóstico. Atención primaria. Diagnóstico.*

Introduction

Parkinson's disease (PD) is a complex multisystemic neurodegenerative disorder affecting over 6 million people globally[1]. PD is hallmarked by their cardinal motor symptoms, but also non-motor symptoms are part of the disease[2,3].

The diagnostic pathway can be divided into three milestones. The first stage is the recognition of the symptoms by the subject. Second, the subject needs to make the decision to seek medical attention. Finally, the primary care physician (PCP) who provides the first contact must suspect and confirm the diagnosis or, if needed, refer the patient to the proper specialist[4]. Research has shown that it takes patients more time to recognize their motor symptoms and to realize they need medical attention, then it takes the general practitioner (GP) to diagnose PD[5]. The median time from motor symptom onset to seeking a PCP has been reported to be around 7-11 months; while the time from the first visit to a final diagnosis varies from 1 to 12 months[4,6].

Factors currently known to delay the diagnosis include young onset of motor symptoms[7], postural instability and gait disorder subtype[4], and female gender[8].

This diagnostic pathway is full of experiences some of them can be negative leading to loss of trust in the doctor, resulting in a lengthy and uncertain process[9]. Benefits of a timely diagnosis include an early initiation of symptomatic treatment, improved functionality, and better quality of life[10]. Data regarding the patient's experiences in their diagnostic pathway are scarce. Gaining insight into the possible factors that delay the diagnosis process may lead to developing effective strategies. This study aims to improve our understanding of the factors involved in each of the stages of the diagnostic pathway of persons with PD (PwP).

Methods

A cross-sectional study was carried out. PwP attending the Movement Disorders Clinic at the National Institute of Neurology and Neurosurgery in Mexico City from July to August 2019 were included in the study. Participants considered for this study were diagnosed with PD using the International Parkinson and Movement Disorders Society clinical criteria[11].

Data collected included demographic variables such as gender, date of birth, current marital, employment status, and years of education, and whether they had any access to social security. A semi-structured questionnaire containing both open-ended and closed-ended questions was designed to assess time form the first identification of motor symptoms to the time of definitive diagnosis. At present, no specific validated questionnaire for this purpose is available for PD, consequently, a questionnaire was designed based on instruments used on other diseases, mainly cancer[12,13]. Selection of the time intervals and main correlated factors was based on critically assessment of literature, conceptual framework, and expert opinion.

A pilot testing was carried out to test the content validity (relevance, acceptability, and feasibility). A total of two rounds of pilot testing were performed. This resulted in changes in the order of the items and clarification of wording or phrasing.

The final questionnaire was divided into three parts. The first part considered the recognition of the initial symptom of PD; PwP provided information regarding their first identified symptom.

The second part included a series of questions that intended to understand the patient's pathway to seek attention with a health-care provider. This section included the time of the first medical consultation, the patient's main reason for seeking for medical attention, selected factors with potential influence on the symptom experience, and healthcare-seeking behaviors. The time of diagnosis, as well as the year of referral to tertiary center, were also collected. Finally, the last part intended to assess the patient's perception on the diagnostic time, if it was considered timely, as well the main reasons for a delayed diagnosis and identified barriers.

In addition, the Movement Disorder Society Unified PD rating scale at the first visit was used to define the motor subtype into tremor dominant (TD), postural instability and gait disturbance (PIGD), and indeterminate according to Stebbins et al.[14] PD onset was classified as classic PD (age of onset 41-59), early-onset PD (EOPD) if age of onset was ≤ 40 years, and late-onset PD (LOPD) if age of onset was ≥ 60 years[15,16].

The index time was defined for the study purposes as the month and year the PwP recalled noticing the motor symptoms associated with the disease for the 1st time. The first milestone collected was externalization defined as the process of thoughts or worries into an external form such as writing or speaking to a third party. The second milestone was seeking medical attention. The last milestone was definitive PD diagnosis. Time between the milestones was measured in months in all cases.

Delay in diagnosis for the study purpose was defined as a span of 12 or more months between the initial recognition of the symptoms and the definitive diagnosis of PD or the beginning of PD treatment[17].

All PwP attending the clinic within the study period were invited to participate. Those who voluntarily agreed to participate were given a full explanation of the study and signed an informed consent form. The study was approved by the local ethics committee.

Statistical analysis

Kolmogorov–Smirnov test was used to test normality. Data were described in measures of central tendency (mean or median) and dispersion as standard deviation (SD) or interquartile range (IQR) accordingly to their distribution. Student's t and analysis of variance (ANOVA) tests were used for the comparison of continuous variables between groups. Mann–Whitney U or Kruskal–Wallis test was used for non-parametric variables analysis. When needed, Bonferroni correction for multiple comparisons was used to adjust the p values. For comparison between categorical variables, Chi-square test was used. Statistical significance was considered as $p < 0.05$.

Results

A total of 66 men (57.9%) and 48 women (42.1%) were included in the study. The mean age was 65.4 ± 12.9 years, and the mean disease duration was 9.5 ± 5.2 years. The mean years of education were 9.7 ± 5.9 years. A total of 76 PwP (66.6%) were married/free union. Fifty-three (46.5%) had access to social security, and only 33 (28.9%) were currently employed. In addition, 24 (21.1%) had a family history of PD.

Regarding PD, a total of 43 PwP (37.7%) were considered classic, 19 (16.7%) EOPD, and 52 (56.6%) LOPD. The most common motor subtype was PIGD (50.9%) followed by TD (36.8%).

Regarding the time elapsed between milestones, the median time from symptom onset to externalization was 1 month with a range of 1-96 months. The median time from the first milestone to seeking medical attention was 2.5 (IQR 10.9) months. The median time from the second milestone to diagnosis was 9 (IQR 14) months. Overall, the median time from noticing the motor symptom onset to the final PD diagnosis was 14.5 (IQR 31) months. Table 1 shows the comparison of the time in months for each milestone according to the main demographic and clinical variables. In summary, age of onset was statistically different across two of the time milestones. PwP with EOPD had a greater time to seek medical attention and time to final diagnosis. For PwP with EOPD, the overall diagnosis pathway (median 48, IQR 57) was longer when compared to the classic onset (median, 15. IQR 32, $p = 0.01$) and LOPD (median 12, IQR 18, $p = 0.01$).

The first part of the questionnaire assessing the recognition of the initial symptom showed that tremor was the most frequent motor symptom noticed by the subject (59.6%) followed by bradykinesia and rigidity (27.2%). Moreover, the main appraisal of the first symptom was being "not worried" (48.2%) followed by "worried or stressed" (43.9%).

The second part of the questionnaire assessed the pathway to seek attention with a health-care provider and final diagnosis. The main reasons for seeking medical attention were symptom worsening (42.1%) followed by symptom onset (29.8%) and symptom persistence (26.3%). The first contact physician was a GP in 36.8%, a movement disorders specialist in 18%, and a general neurologist also in 18% of the cases. The specialty of the first contact physician did not had an impact on the time from the first medical consultation to the PD diagnosis ($p = 0.16$).

Finally, the third part of the questionnaire assessed the PwP perception on the diagnostic time and its timeliness. A total of 54 (47.4%) PwP were timely diagnosed according to the study criteria, while 60 (52.6%) had a delay on diagnosis. The only variables with a statistically significant difference between groups were age and age at onset. PwP timely diagnosed were older

Table 1. Time milestones (months) according to the main demographic and clinical variables of the study sample

Variables	Time to externalize Median (IQR)	Time to seek medical attention Median (IQR)	Time to diagnosis Median (IQR)
Gender Median (IQR)			
Male (n = 66)	1 (0.25)	6 (11.25)	14 (30)
Female (n = 48)	1 (0)	5 (11)	14.5 (42)
p†	0.244	0.654	0.858
Age at onset Median (IQR)			
Classic (n = 43)	1 (3)	7 (13)	15 (32)
EOPD (n = 19)	1 (0)	18 (20)	48 (57)
LOPD (n = 52)	1 (0)	2 (11)	12 (18)
p‡	0.177	0.003	0.006
Family history Median (IQR)			
None (n = 82)	1 (0)	6 (11)	12.5 (30)
Parkinson's disease (n = 24)	1 (0)	5 (11)	14.5 (50)
Essential tremor (n = 8)	1 (0)	13 (39.75)	27 (79)
p‡	0.722	0.474	0.235
Comorbidities Median (IQR)			
No (n = 68)	4.6 ± 13.8	13.4 ± 17	30.6 ± 31.5
Yes (n = 46)	2.8 ± 4.5	12.2 ± 23.8	25.1 ± 30.8
p†	0.94	0.19	0.25
Motor subtype Median (IQR)			
PIGD (n = 58)	1 (0)	6 (18.5)	12 (26)
Tremor dominant (n = 42)	1 (0.25)	4.5 (11)	16 (31)
Indeterminate (n = 14)	1 (6.5)	12 (10.25)	30.5 (60)
p‡	0.238	0.692	0.150
Education (years) Median (IQR)			
< 12 (n = 71)	1 (0)	7 (13)	13 (30)
≥ 12 (n = 43)	1 (0)	4 (11)	18 (42)
p†	0.301	0.122	0.879

EOPD: early-onset Parkinson's disease; IQR: interquartile range; LOPD: late-onset Parkinson's disease; PIGD: postural instability and gait disturbance.
†Mann–Whitney U-test; ‡Kruskal–Wallis test.

(68.4 ± 11.1 vs. 62.7 ± 13.9, p = 0.02) and had an older age of onset (59.7 ± 12.4 vs. 52.4 ± 14.7, p = 0.01).

Finally, patient's perception on the diagnostic time was reported as very adequate/adequate in 52.7%, average in 21.1%, and inadequate/very inadequate in 26.3%. When comparing those PwP with a time from onset to diagnosis < 12 months with those ≥ 12 months, no statistically significant difference was found in the very adequate/adequate perception (61.1% vs. 45%, p = 0.13). Similarly, no statistical difference was found regarding the very inadequate/inadequate perception between groups (22.2% vs. 30%, p = 0.47). Moreover, the percentage of agreement between very adequate/adequate perception and actual time to diagnosis < 12 months was only 50%.

The main reason for a delayed diagnosis given by those PwP who responded average or worst (n = 54) was misdiagnosis in 63%, followed by economical constraints in 11.1%, belief of spontaneous symptoms relief in 7.4%, and lack of interest by the PwP in 7.4%.

On the other hand, the main barriers that might have delayed seeking medical attention identified by the PwP were belief of spontaneous symptoms relief in 28.9%, lack of trust in their doctor in 17.6%, fear of a diagnosis in 11.4%, and limited access to health services in 7.9%. Table 2 compares the main factors assessed in the questionnaire between PwP diagnosed before or after 1 year from symptom onset.

Discussion

PD is a chronic neurodegenerative disease affecting activities of daily living as well as the health-related quality of life of the persons with the disease. While no cure has been found yet, it has been shown that symptomatic treatment has a benefit in the PwP life, thus supporting the need for an earlier diagnosis[10]. The diagnostic pathway begins in the patient's end by recognizing the symptoms, acknowledging their relevance, and deciding to seek medical consultation. On the

Table 2. Comparison of healthcare-seeking behaviors and patient's perception on the diagnostic pathway according to the time from onset to diagnosis

Variables	Time from onset to diagnosis ≤ 1 year	Time from onset to diagnosis > 1 year	p†
Symptom at onset			
Tremor	31 (57.4)	37 (61.7)	0.64
Rigidity/bradykinesia	16 (29.6)	15 (25)	0.99
Gait disorder	3 (5.6)	2 (3.3)	0.56
Symptom appraisal			
Not worried	24 (44.4)	31 (51.7)	0.44
Worried/stressed	27 (50)	23 (38.3)	0.21
Fear	2 (3.7)	5 (8.3)	0.30
Other	1 (1.9)	1 (1.7)	0.94
Reason for seeking medical care			
Symptom onset	26 (48.1)	8 (13.3)	<0.001
Symptom persistence	15 (27.8)	15 (25)	0.74
Symptom worsening	12 (22.2)	36 (60)	<0.001
Other	1 (1.9)	1 (1.7)	0.94
First contact physician			
General practitioner	18 (33.3)	24 (40)	0.46
Internist/geriatrist	3 (5.6)	4 (6.7)	0.80
Neurologist	13 (24.1)	13 (21.7)	0.76
Movement disorder specialist	14 (25.9)	12 (20)	0.45
Other	6 (11.1)	7 (11.7)	0.93
Previous knowledge of the disease			
Yes	32 (59.3)	28 (46.7)	0.18
No	22 (40.7)	32 (53.3)	0.18
Diagnostic time perception			
Very inadequate	6 (11)	8 (13.3)	0.71
Inadequate	6 (11.1)	10 (16.7)	0.39
Acceptable	9 (16.7)	15 (25)	0.29
Adequate	20 (37)	17 (28.3)	0.32
Very adequate	13 (24.1)	10 (16.7)	0.33

†Chi-square test.

other hand, the journey to diagnosis ends at the doctor's side with a definitive diagnosis and the therapeutic shared decision-making. Nevertheless, between these two milestones, there are several, sometimes burdensome, factors that can result in a diagnosis delay. We aimed to identify some of these factors resulting in a timely or delayed diagnosis in PwP.

In our study, the time from symptom onset to the diagnosis of PD had a median of 14.5 months which is within the range reported in the literature which is between 12 and 19 months.

The demographic and clinical determinants of the diagnosis delay reported in the literature include gender, age at onset, and motor subtype. Regarding gender, some authors report a longer time in men compared to women[4], while other have found no difference[8]. Interestingly, Vlaanderen et al. reported similar finding stating that while no significant differences were found in neurologist consultations, women with PD visited GP more often than men[17]. In our study sample, no difference in the diagnosis pathway between men and women was found. It has also been reported that PwP with PIGD subtype had a longer time to seek medical care[4]. In our study, no difference in the time to seek medical care between motor subtypes was found. Finally, a longer time to diagnosis has been reported in PwP with EOPD ranging from 25 to 60 months[18-20]. Our study confirmed this finding. This can be partially explained by the still common believe, in both general population and health providers, that PD is a disease only seen in the elderly, thus not considering the possibility, and delaying medical consultation. Another point to consider is that tremor in younger persons has more differential diagnosis, such as essential tremor, requiring longer diagnosis work-up process.

Regarding the symptom recognition, tremor was the most common symptom identified which might be

expected since it can usually be more easily identifiable by the patient and their family. Interestingly, the most common appraisal was being now worried in almost have of the patients. Providing better health education might lead to improvement in this stage of the diagnosis pathway.

Regarding the reasons for seeking medical attention, symptom worsening rather than its onset or persistence was the most reported by the PwP. Again, rising awareness of the relevance of the onset and persistence of parkinsonism and tremor is needed. Almost 40% of the subjects went to GP, while 36% went to neurologist/movement disorder specialist. The choice of the first contact health provider did not had an impact in the time to diagnosis, although it might have been expected it to be shorter in the specialist group. It might be possible that PwP seen by a GP had the full-blown clinical picture while those attending a specialist had a more atypical presentation, but our study design does not allow to reach that conclusion and further studies on this matter are needed.

Regarding the perception of the time to diagnosis, half of the PwP reported a very adequate/adequate. In contrast, Plouvier et al. reported that only 4.8% of their patients reported being satisfied with their diagnosis pathway[9]. This striking difference is probably the result of different constructs; Plouvier et al. assessed the satisfaction with the whole diagnostic pathway. In contrast, our study assessed the perception of the amount of time from symptom onset to diagnosis. More studies using a standardized measure are needed on this matter. In addition, the percentage of agreement between the study definition of a timely diagnosis and a positive perception by the PwP was only 50% which highlights the difficult of this construct as Rees et al. have stated[10].

When the PwP considered the diagnosis not being timely, the main reason was misdiagnosis in over 60%. Unfortunately, the number of doctors or number of diagnosis received before PD was not assessed in our study. Still, misdiagnosis rate as reported by the PwP was remarkably high underscoring the need for better training at the health provider end. Other reasons attributable to the PwP were belief of spontaneous symptoms relief and lack of interest but their frequency was much lower.

Finally, the barriers delaying the diagnosis identified by the PwP also included the belief of spontaneous symptoms relief in a third of the cases, but also lack of trust in their doctor. Patient-doctor relationship and shared decision-making are a critical part of the diagnosis pathway; also, it has been reported that when PwP gets engaged in the process of their disease, correlates to a greater quality of life[21-23].

Our study has limitations. First, the lack of a disease specific validated tool for PD; our questionnaire was based and adapted from instruments used in other diseases. Efforts should be taken in developing these tools for PwP exploring more in depth some of the issues highlighted in our study. Second, recall bias cannot be avoided with some variables, such as the time of first motor symptom and the time of PD diagnosis. Some cases were diagnosed at our center but other were diagnosed elsewhere and then referred.

Conclusion

Factors in both the PwP and the doctor side play a role in delaying the diagnosis. Improving awareness of the disease as well as improving medical education are needed. The diagnosis pathway in PD can be improved with combined efforts by the PwP and the health providers that should lead to a shorter time to diagnosis and better quality of life.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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