J Neurol (2013) 260:1978–1981
DOI 10.1007/s00415-013-6905-3

ORIGINAL COMMUNICATION

Determinants of delayed diagnosis in Parkinson's disease

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Received: 30 January 2013 / Revised: 18 March 2013 / Accepted: 27 March 2013 / Published online: 10 April 2013

Abstract The early and accurate diagnosis of Parkinson's disease (PD) is the first step towards optimal patient management. The aim of this study was to investigate the major determinants of delayed diagnosis in PD. We recruited a population-representative cohort of 239 newly-diagnosed PD patients who underwent clinical and neuropsychological evaluation. Non-parametric methods were used to define the factors associated with diagnostic delay. The median time from motor symptom onset to primary care physician (PCP) presentation was considerably longer than the time from PCP presentation to PD diagnosis (11 vs. 1 months). Male sex and presenting motor phenotype were independently associated with delayed PCP presentation on Cox regression analysis. Patients presenting with gait disturbance experienced the longest delay, whilst those presenting with tremor had the shortest. In summary, male sex and presenting motor phenotype are key determinants of delayed diagnosis in PD.

Keywords Diagnosis · Delay · Parkinson's disease · Gender

Introduction

The early diagnosis of Parkinson's disease (PD) is desirable in order to advise patients about their likely prognosis and initiate treatment where appropriate. This is particularly important as we enter the era of disease-modifying drug trials, where the goal is increasingly to intervene in the earlier stages of disease.

The journey from symptom onset to PD diagnosis depends on several key 'filters' [1]. Firstly, patients and those around them must identify the symptoms as being abnormal, prompting them to seek advice from their primary care physician (PCP). Secondly, the PCP must recognise the presenting complaint as being compatible with PD and make an appropriate referral to a movement disorders specialist. Thirdly, the specialist must make a timely and accurate diagnosis, with or without the help of investigations. Each of these steps may be influenced by a multitude of factors.

The aim of this study was to investigate the major determinants of delayed diagnosis in a population-representative cohort of newly-diagnosed PD patients.

Methods

Patients were recruited to the PICNICS study (Parkinsonism: Incidence and Cognitive Heterogeneity in Cambridgeshire) between January 2008 and July 2011. They were referred either directly from their PCP (where there was no established diagnosis and this was made at the baseline PICNICS assessment) or a specialist (where the diagnosis had already been made). The study was approved by the Cambridgeshire Research Ethics Committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later

Electronic supplementary material The online version of this article (doi:10.1007/s00415-013-6905-3) contains supplementary material, which is available to authorized users.

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amendments. All patients gave their informed written consent prior to inclusion in the study.

Three hundred and forty-three patients were referred during the study period. Seventy patients were deemed by study investigators to have alternative diagnoses (Table 1). Twenty-two patients with 'unspecified parkinsonism' were excluded because they did not fulfil UK Brain Bank diagnostic criteria for PD [2]. Twelve patients were excluded because they were not incident cases. Therefore, 239 patients were included in the final analysis. In terms of diagnostic delay, there were no significant differences between patients referred by their PCP ($n = 58$) or a specialist ($n = 181$); therefore, they were analysed together. Clinical characteristics of the cohort are shown in Table 2.

Detailed clinical history was available for all patients including date of motor symptom onset, PCP presentation and PD diagnosis. Times between motor symptom onset/PCP presentation and PCP presentation/PD diagnosis were rounded to the nearest month. Presenting motor phenotype was documented at the time of the initial PICNICS visit based on the predominant complaint that prompted the patient to visit their PCP (46 % tremor, 19 % motor impairment including micrographia, 18 % gait disturbance, 10 % limb/axial rigidity and 8 % global bradykinesia). These five motor phenotype categories were chosen at the outset of the study. In those patients with asymmetric motor symptoms, we documented whether the dominant or non-dominant side was affected. Smoking history, family history, age of leaving full-time education and non-PD medications were noted. Comorbidities were grouped into six categories (visual, neurological, psychiatric, vascular, musculoskeletal and medical) using the same approach as Marrie et al. [3], who previously studied the impact of comorbidities on diagnostic delay in multiple sclerosis. Total daily levodopa equivalent dose (LED) was calculated using the formula proposed by Tomlinson et al. [4].

Patients underwent a variety of clinical assessments at their baseline PICNICS visit including tests of motor disability [Unified Parkinson's Disease Rating Scale (UPDRS) part III], cognition [Addenbrooke's Cognitive Examination (ACE-R)], mood [Beck Depression Inventory (BDI)], sleep [Pittsburg Sleep Quality Index (PSQI)], quality of life [Parkinson's Disease Questionnaire (PDQ-39)] and apathy [Apathy Evaluation Scale (AES)].

Non-parametric methods were used to investigate the demographic and clinical factors associated with diagnostic delay. Mann–Whitney (two groups) and Kruskal–Wallis (more than two groups) tests were used for categorical variables. Spearman rank correlation coefficient was calculated for continuous variables. We then went on to construct a series of multivariate Cox regression models for variables that were found to be significantly associated with diagnostic delay.

Table 1 Non PD diagnoses in patients referred to the PICNICS study

Alternative diagnosis	Number of patients
Essential tremor	24
Drug-induced parkinsonism	10
Dementia with Lewy Bodies	7
Dystonic tremor	4
Vascular parkinsonism	4
Myopathy	3
Alzheimer's disease	3
Neuropathy	3
Orthostatic tremor	2
Physiological tremor	2
Multiple System Atrophy-Parkinsonism	1
Focal dystonia	1
Other[a]	6

[a] Unspecified gait disturbance ($n = 3$), gait disturbance secondary to brain irradiation and chemotherapy ($n = 1$), generalised anxiety disorder ($n = 1$) and osteoarthritis ($n = 1$)

Results

The median time from motor symptom onset to PCP presentation was 11 months (interquartile range 6–18 months, range 0–100 months). This was considerably longer than the time from PCP presentation to PD diagnosis, where the median time was 1 month (interquartile range 0–4 months, range 0–53 months).

Motor symptom onset to PCP presentation

Median time to PCP presentation was longer in men compared to women (12 vs. 8 months, $p = 0.005$). There was a significant difference in time to PCP presentation depending on the presenting motor phenotype ($p = 0.016$)—patients presenting with gait disturbance or global bradykinesia experienced the longest delay, whilst those presenting with tremor or limb/axial rigidity had the shortest. Age of symptom onset, dominant versus non-dominant side affected, cohabitation or retirement status, age of leaving full-time education, smoking history, family history, presence of comorbidities and number of non-PD medications were not associated with time to PCP presentation. There were no associations between time to PCP presentation and clinical parameters such as UPDRS part III, cognition, mood, sleep, quality of life or apathy. Gender and presenting motor phenotype remained significantly associated with delayed PCP presentation on Cox regression analysis, even after taking into account covariates (Supplementary Figs. 1 and 2, respectively). The beta coefficient for male

Table 2 Demographics and clinical characteristics of our cohort

Variable	Median (interquartile range)
Male sex (%)	62
Age at symptom onset	67 (66–73) years
Positive family history[a] (%)	10
White British ethnic origin[b] (%)	98
Married or cohabiting (%)	78
Retired (%)	74
On dopaminergic replacement therapy[c] (%)	42
LED (if treated)	300 (150–420) mg
UPDRS III score	31 (23–38)
Hoehn and Yahr stage	2 (1–2)
ACE-R score	90 (86–94)

[a] ≥1 first degree relative with idiopathic PD

[b] Others from Sri Lanka ($n = 1$), Bangladesh ($n = 1$), India ($n = 1$), Poland ($n = 1$)

[c] 24 % levodopa, 8 % ropinirole, 8 % pramipexole, 4 % rasagiline

sex was 1.37 (95 % CI 1.04–1.81, $p = 0.027$), whilst the beta coefficient for gait disturbance versus tremor was 1.69 (95 % CI 1.15–2.48, $p = 0.007$).

PCP presentation to PD diagnosis

The median time from PCP presentation to PD diagnosis was also influenced by presenting motor phenotype ($p = 0.040$)—patients presenting with limb/axial rigidity experienced the longest delay, whilst those presenting with global bradykinesia had the shortest. After stratification by median age of symptom onset (67 years), we found that older patients with psychiatric comorbidity took significantly longer to be diagnosed following PCP presentation, as did patients with apathy (patient and carer-completed AES) ($p = 0.013$ and $p = 0.002$, respectively). Otherwise, no clinical parameters were associated with time to PD diagnosis. None of these factors remained significant on Cox regression analysis.

Gender-related differences in clinical characteristics

We carried out an exploratory analysis but found no significant differences in clinical characteristics between men and women at presentation.

Discussion

We have shown that the time taken for PD patients to consult their doctor in the community is the longest link in the diagnostic chain, on average taking around 11 months from motor symptom onset. This is broadly similar to other European countries [5] and has implications for strategies designed to aid earlier identification of patients. As well as instructing PCPs about PD symptomatology, our results indicate that it may be more important to educate patients and encourage them to seek advice earlier from their PCP.

It is not surprising that patients and doctors have greater difficulty recognising certain PD features. Early gait dysfunction, for example, can be subtle and non-specific, often attributed to normal ageing or medical conditions such as osteoarthritis.

We observed a significant difference in the time to PCP presentation in men (12 months) compared to women (8 months). Saunders-Pullman et al. [6] previously found that women with PD had a slightly longer, but statistically non-significant, delay from symptom onset to first physician visit in their pilot study. We initially wondered whether differences in clinical presentation may have influenced individual's decision to seek medical advice. Haaxma et al. [7] reported that women were two years older at symptom onset, more likely to present with tremor dominant disease and had less nigrostriatal dysfunction compared to men. However, we found no gender-related differences in clinical characteristics in our study, suggesting that the independent relationship between male sex and delayed PCP presentation reflects differences in health care-seeking behaviour.

The notion of men being reluctant to consult their doctor is not new [8] and is supported by UK population survey evidence showing less than half the number of PCP visits in men compared to women [9]. The barriers to men consulting their doctor are not well understood but may include poor knowledge about health-related matters, under-reporting of symptoms and the pressure to conform to traditional masculine stereotypes. Possible solutions to overcoming these barriers include targeted advertising campaigns towards men, opportunistic neurological screening during routine health checks, and non-traditional healthcare delivery (e.g. in the workplace or out of office hours).

Our study benefited from a large cohort of newly-diagnosed PD patients close to the time of diagnosis. We hope that this helped to minimise recall bias, especially since we gathered information from a variety of sources (including patient, partner, family members, primary care letters and hospital records). Patients were assessed in either the specialist research clinic or their own home, ensuring that our cohort was truly representative.

We should highlight that this study was not designed specifically to investigate diagnostic delay in PD, rather it was part of a community-based epidemiological study. We did not take into account other possible explanations for

delayed diagnosis such as referral to the wrong specialty, time taken whilst waiting for investigations or initial misdiagnosis by the specialist. Furthermore, we focussed on PD motor symptoms since it is invariably these which trigger PCP consultation and, ultimately, diagnosis. Of course, these can be preceded by non-motor symptoms—often by several years—and one previous study found that patients presenting with purely non-motor symptoms took longer to be diagnosed [10]. Ideally, we need reliable biomarkers capable of diagnosing PD in the pre-motor phase, but until they exist we will continue to rely on the timely identification of motor symptoms in the community and this study provides new data in this regard.

In conclusion, we have identified key determinants of diagnostic delay in PD—male sex and presenting motor phenotype—which should be addressed to ensure that PD patients are identified and diagnosed as soon as possible.

Acknowledgments This work was supported by a NIHR Biomedical Research Award to Addenbrooke's Hospital/University of Cambridge, as well as grants from Parkinson's UK, Cure Parkinson's Trust and the Van Geest Foundation. DPB and JRE have been recipients of a Raymond and Beverly Sackler studentship.

Conflicts of interest The authors declare that they have no conflicts of interest.

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