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Original article

Parkinson's Disease and development of levodopa induced motor complications: Influence of baseline features and first medical approach

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ABSTRACT

Background: The introduction of levodopa in clinical practice represents a hallmark in the treatment of the neurodegenerative disease, Parkinson's Disease. However, levodopa induced motor complications, namely dyskinesias and motor fluctuations, develop in the majority of Parkinson's Disease patients.
Objective: to identify which Parkinson's Disease's, patient's and therapeutics' initial features are more associated with dyskinesias or motor fluctuations development.
Methods: Patients with diagnosed Parkinson's Disease attending neurology outpatient clinic at Centro Hospitalar São João were selected. For this observational study, data was retrospectively collected from patient's clinical records. A survival analysis model with univariate and multivariate regression analysis was used.
Results: 87 patients with a mean of 72 ± 9.7 years were included. After a median follow-up of 6 (range 1–17) years, 35.6% patients developed dyskinesias; and with a median of 5 (range 1–16) years, 32.2% developed motor fluctuations. After multivariate analysis, the akinesia/rigidity subtype was found to have a higher risk of dyskinesias and motor fluctuations development. Age of onset ≤50 years was associated with motor fluctuations development.
Conclusion: In conclusion, our results suggest that Parkinson's Disease patients' initial characteristics, such as subtype or age of onset, are independently associated with the development of motor complications.

Introduction

Parkinson's Disease (PD) is a neurodegenerative disorder described in 1817 by James Parkinson.[1] Since his publication, "An Essay on Shaking Palsy",[1] there has been a crescent scientific interest on this subject. According to the most accepted theory, it was suggested that PD has a spreading character correlated with deposition of abnormal aggregates which create a significant loss of dopaminergic enervation in Substantia Nigra pars compacta.[2] Motor symptoms begin when loss in dopamine uptake becomes ≥50%.[3]

In clinical practice, main symptoms are muscular rigidity, rest tremor and/or postural instability.[4] One of the most common and simplest used scales to assess motor progression and severity of PD is the Modified Hoehn and Yahr Scale (H&Y).[5]

As a definitive solution is yet to be found, treatment can be the most challenging phase. General measures can reduce the impact of motor symptoms, but not completely, and surgical treatments are indicated in advanced disease[6,7]; differently, pharmacological therapy is widely used.[8] Many drug classes are available – such as MAO-B inhibitors, dopaminergic agonists (DA) and anticholinergic drugs – but the best drug in relieving motor symptoms is levodopa.[9,10] Associations with aromatic L-amino acid decarboxylase inhibitor and catechol-O-methyltransferase inhibitors are used

Abbreviations: AR, Akinesia/rigidity; CI, confidence interval; DA, dopaminergic agonists; DFS, dyskinesias-free survival; DK, dyskinesia; MC, motor complications; MF, motor fluctuation; MFFS, motor fluctuations-free survival; PD, Parkinson's Disease; TD, tremor dominant.

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to optimize drug action and reduce side effects like nausea and vomiting.[11]

With the risk of undertreatment, levodopa introduction is sometimes delayed because of the most feared levodopa-induced motor complications (MC): dyskinesia (DK) and motor fluctuations (MF).[12]

MF include "wearing-off" phenomena - symptoms re-appearance just before the next levodopa dose – and generally it is the first MC. MF also include "on-off" phenomena – sudden changes between normal and parkinsonic motor state; and "delayed on" phenomena – when symptoms relief takes longer.[12,13]

DK are defined as involuntary movements, the most common are chorea and dystonia, that can affect any body region, usually an extremity.[12] This region can coincide with the first one affected by motor symptoms of PD.[13] Initially they are peak-dose related, but can also be dysphasic – according to levodopa blood levels rise and fall – or "off dyskinesias" – when these levels are low.[13,14]

Although less and later than in the past, nowadays a significant part of PD patients develop these MC: 9 or more years after beginning levodopa, close to 90% of patients will develop DK and 70% MF.[15] In Portugal, it was reported that patients with MF have 2 times more socio-economic costs than MF-free patients.[16] Also, quality of life is greatly impaired in PD patients with MC. Their mobility, daily living activities or communication skills can be compromised, and stigmatization is frequent.[17]

MC are important obstacles to the everyday life of PD patients. It is vital not only to understand their etiology and pathophysiology, but also to understand what can be made to prevent them right since the first medical approach.

Our objective was to identify which Parkinson's Disease's, patient's and therapeutics' initial features are more associated with dyskinesias or motor fluctuations development.

Methods

Study design

This is an observational, analytical, non-interventional, non-comparative, retrospective, longitudinal study. It took place in a central university hospital, Hospital São João, Porto, Portugal.

Source of information were clinical records of patients followed in the hospital's outpatient clinic by two movement disorders neurologists (C.G. and M.J.R.) in periodic appointments.

The research protocol was certified by the ethical committee of Faculty of Medicine of Porto University and by the ethical committee of Hospital São João, respecting the Declaration of Helsinki principles.

Patient selection

Patients were selected according to the following inclusion criteria: appointments in Hospital São João outpatient's clinic, diagnosis of PD, and attendance of at least two appointments of movement disorder since 2012. In these appointments, the diagnosis of PD is based on UK Parkinson's Disease Society Brain Bank.[4]

Patients who had secondary causes of parkinsonism, uncertain diagnosis, missing data about first pharmacological therapy, levodopa not included in therapy, follow-up time less than 3 years or previous treatment with neurosurgical treatment, were excluded.

Data collection

Each patient's entry date was the year of first appointment and, for all, follow-up ended in August 2014. No blinding procedures were needed.

To gather all the information, a database was created using Microsoft Office Excel 2007. The studied variables were: gender, age at symptoms onset, time between symptoms onset and diagnosis, PD subtype at onset (tremor dominant (TD), Akinesia/rigidity (AR) or mixed), H&Y class at levodopa onset, time between DA onset and levodopa onset, initial drug (levodopa, DA or other), evolution of first year levodopa dose, presence of MF and/or DK and time since levodopa onset until the occurrence of MF and/or DK. The last one was used as our dependent variable.

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics 22 according to a survival model. Dyskinesias-free survival (DFS) and Motor fluctuations-free survival (MFFS) were defined as the time from levodopa onset until the occurrence of DK or MF, respectively, or the most recent follow-up. Patients without DK or MF were censored in the last follow-up date. Continuous variables were expressed as the median, percentile 25 (p25) and percentile 75 (p75). For further data analyses, these variables were categorized.

A Kaplan–Meier estimate was used to calculate the median survival time and survival rate free of each MC. Outcome predictors were evaluated using univariate and multivariate Cox proportional regression analysis. Multivariate analysis was used to account for confounding variables; the ones included were those with a significance of $p < 0.20$ in univariate analysis. Results were expressed as hazard ratio (HR) with 95% confidence interval (CI). A p-value <0.05 was used as criteria for statistical significance in the multivariate model.

Results

Baseline features

After applying inclusion and exclusion criteria, 87 patients were included in this study. Patients excluded for not having levodopa included in their therapy, did not develop MC, until follow-up ended.

General features from study population are described in Table 1.

Table 1
General features.

Feature	$n = 87$
Gender	
Male	44 (50.6%)
Female	43 (48.4%)
Age (mean (SD))	71.8 (9.7)
Age at symptoms onset, (mean (SD))	60.76 (10.0)
≤50	11 (12.6%)
51 and 60	35 (40.2%)
>60	41 (47.1%)
Time until diagnosis (mean (SD))	1.6 (0.8)
Parkinson's Disease Subtype	
Tremor dominant	45 (51.7%)
Akinesia/rigidity	32 (36.8%)
Mixed	10 (11.5%)
1st Drug	
Dopaminergic agonist	38 (43.7%)
Levodopa	47 (54.0%)
Other	2 (2.3%)
H&Y at levodopa onset, (median (range))	2 (1–4)
Motor Complications	45 (51.7%)
Dyskinesias	31 (35.6%)
Motor Fluctuations	28 (32.2%)

SD, standard deviation; H&Y, Hoehn and Yahr class.

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