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Later age at onset in Parkinson's disease over twenty years in an Italian tertiary clinic

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ABSTRACT

Background: Age is considered an important risk factor for Parkinson's disease (PD). However, although life-expectancy has increased considerably, incidence rates of PD appeared to be stable over the last two decades. Accordingly, an increase in mean age at onset over time could be expected. We investigated the changes in age at onset in PD over the last two decades.
Methods: All consecutive PD patients assessed over a 18-year period (1995–2013) in a single tertiary outpatient clinic were included in the present retrospective cohort study.
Results: After adjusting for several confounders (gender, positive family history for PD, education, smoking at onset and past exposure to environmental/occupational pollutants), 5-year cohorts of year of disease onset were associated with increasing age at onset in both prevalent ($N = 6996$) and incident ($N = 4172$) cases (for trend, $P < 0.001$). From 1995–2000 to 2010–2013 there was an increase in predicted age of 4.1 years (95% CI, 3.0–5.2) and 3.9 years (95% CI, 2.7–5.1) in prevalent and incident cases, respectively. However, the change in predicted age at PD onset, across cohorts of year at onset, showed a steeper increase than the corresponding sex and cohort-matched mean age from the official Italian statistics.
Conclusions: Over the last two decades, age at onset of PD appeared to shift progressively towards more advanced age. However, sequential, high-quality population-based incidence studies are required. To establish whether there is a trend towards increase in age at onset over and above general population ageing and to assess whether the increase is associated with improved medical and socio-economic conditions.

1. Introduction

Aging is a major risk factor for Parkinson's disease (PD) [1,2]. However, age-related decline in the number of dopaminergic neurons [3] does not appear to fully account for its occurrence. The etiology of PD is not well understood and the hypothesis of a multifactorial origin (the so-called multiple-hit hypothesis) is supported by findings from several case-control and prospective studies focusing on genetic and environmental factors, lifestyle habits and comorbidities [2,4–8]. Since the last century, living and socio-economic conditions have improved considerably and the increase in mean life-expectancy [9] may be a direct consequence. With increasing age, incidence and prevalence of PD would be expected to increase accordingly. However, recent primary care-based analyses have found that incidence rates have been substantially stable over the last two decades [10,11]. To date, there are no studies that have evaluated the trend of the age at onset of Parkinson's disease. Accordingly, we investigated whether age at PD onset has changed over the last two decades in an Italian tertiary outpatient clinic. This information may suggest the need of more laborious incidence studies, the results of which could be

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useful to improve health policies and the estimation of future epidemiologic data and utilization of Healthcare Systems economic resources.

2. Methods

2.1. Data source

We conducted a population-based, retrospective, cohort study using the Parkinson Institute-Milan (Italy) research database, which contains computerized demographic, lifestyle information and general medical information and disease-specific records from patients assessed at the center for disease diagnosis and management. The Parkinson Institute (Milan, Italy) is a nationally recognized movement disorders clinic (tertiary clinic) located in the Lombardy region of the North of Italy. Patients attending this Institute come from throughout the country (Supplementary Fig. 1), in addition to the Lombardy region (actual population of Lombardy: ~10.000.000 inhabitants, with approximately 20% of total PD cases from this region attending the Parkinson Institute) [12,13].

2.2. Subject selection

Only patients with a diagnosis of probable idiopathic PD were considered. Diagnosis was based on the UK PD Society Brain Bank criteria established in 1992 [14]. Therefore, in order to avoid any possible diagnostic bias, we limited the extraction of data to cases reporting PD onset after 1995.

2.3. Study variables

Ascertainment of demographic, lifestyle information and general medical information and disease-specific records on all patients admitted to the institute was performed by means of a self-administered questionnaire, and confirmed through direct interviewing by a neurologist experienced in movement disorders. In particular, age at onset was defined as the time when one of the cardinal signs was first noted.

Information on the following covariates was also extracted: birth date, gender, family history, education, smoking status (categorized as current, former/never according to age at onset), exposure to environmental/occupational pollutants (exposure [either occupational or nonoccupational] to any type of pesticide, solvent or carbonylic compound and/or rural living) [6,15], region of residence and disease duration at the first visit.

2.4. Statistical analyses

Patients were stratified by 5-year cohorts of year of onset. Continuous variables were reported as mean and standard deviation (normal distribution) or median and inter-quartile range (non normal distribution; 25th–75th percentile [interquartile range, IQR]), while categorical variables were presented as counts and percentages.

The association between age at onset and cohort of year of onset was assessed by means of univariate and multivariate regression models including gender, positive family history for PD, education, current smoking and exposure to environmental/occupational pollutants as covariates. Model adequacy was assessed graphically by inspection of residual. Before confounders were included in the models, collinearity between all possible covariates was assessed. Two sets of analysis were considered. Primary analyses were based on prevalent cases. Then, in order to avoid confounding associated with potential recall bias, secondary analyses were performed by refitting the original models on incident cases (disease duration at first assessment $\leq$3 years). Sensitivity analyses were performed on prevalent and incident cases of the following patient population sub-groups: age at onset $\geq$40 years; no exposure to pollutants; negative family history; living in the region of Lombardy. The interaction between covariates was also investigated.

Finally, trends in the adjusted predicted age at onset across cohorts of year at onset were plotted and informally compared with the sex and cohort-matched mean age from the official Italian statistics [16]. To minimize the confounding effect of early-onset cases, who are more likely to have a genetic basis and to be referred to a tertiary clinic known for a PD-related Biobank, we limited the comparison to cases aged at onset $\geq$40 years and subjects aged $\geq$40 years.

All statistical analyses were performed using STATA 13 statistical software (StataCorp, College Station, TX, USA). The level of significance was established in a two-tailed P-value <0.05.

2.5. Ethics

The study was performed in agreement with the principles of the Declaration of Helsinki and the local Ethics Committee was notified in compliance with Italian legislation on retrospective studies. We obtained written informed consent from every patient recruited.

3. Results

Since 1995 up to March 2013, 7083 patients with a confirmed clinical diagnosis of PD were assessed. Of these, 87 had incomplete data. Accordingly, the final study population consisted in 6996 prevalent (median disease duration, 3 years [IQR, 1–5]) and 4172 incident cases, (median disease duration, 2 years [IQR, 1–2]).

The features of the study population are presented in Table 1. Prevalent and incident cases presented similar characteristics. Over the last two decades, we observed a slight increase in the number of patients reporting a positive family history for PD and a progressive reduction in those previously exposed to environmental/occupational pollutants and reporting smoking at onset.

Cohort of year of disease onset was associated with increasing age at onset in both prevalent and incident cases (Table 1, Fig. 1-Plot A and Supplementary Fig. 2). The same applied to cases with age at onset $\geq$40 years (Fig. 1-Plot B). The association between age at onset and the year of onset was confirmed also after adjustment for several confounders. From cohort 1995–2000 to 2010–2013 there was an increase of 4.1 years (95%CI, 3.0–5.2) and 3.9 years (95%CI, 2.7–5.1) in prevalent and incident cases, respectively. In multivariable analysis, earlier age at disease onset was observed also in patients reporting positive family history for PD, higher education, exposure to pollutants and active smoking ($P < 0.001$ for all; Table 2 and Table 3). All sensitivity analyses refitted on patients with age at onset $\geq$40 years (prevalent cases, $N = 6831$; incident cases, $N = 4086$) or not exposed to pollutants (prevalent cases, $N = 6502$; incident cases, $N = 3850$) or reporting a negative family history

Table 1
Descriptive statistics of the study population by cohorts of year of Parkinson's disease onset.

Cohorts						
All		1995–1999	2000–2004	2005–2009	2010–2013	*P*-value[a]
Prevalent cases [N]	[6996]	[1903]	[2448]	[2147]	[498]	
Age at onset (years), Median (IQR)	63 (56–69)	60 (54–67)	63 (55–70)	65 (57–71)	65 (58–72)	<0.001
Men, %	57	58	57	57	60	0.974
Positive family history, %	13	12	13	14	12	0.140
Smoker at onset, %	9	15	8	6	8	<0.001
Exposure to pollutants, %	7	14	7	2	5	<0.001
Education (years), Median (IQR)	8 (5–13)	8 (5–13)	8 (5–13)	11 (8–13)	13 (8–14)	<0.001
Incident cases [N]	[4172]	[755]	[1258]	[1661]	[498]	
Age at onset (years), Median (IQR)	64 (56–70)	61 (55–68)	64 (56–70)	65 (57–71)	65 (58–72)	<0.001
Men, %	57	58	58	56	60	0.976
Positive family history, %	12	8	12	14	12	0.001
Smoker at onset, %	10	22	10	6	8	<0.001
Exposure to pollutants, %	8	22	9	2	5	<0.001
Education (years), Median (IQR)	8 (5–13)	8 (5–13)	8 (5–13)	11 (8–13)	13 (8–14)	<0.001

Abbreviations: IQR, interquartile range.
[a] For trend over cohorts of year of onset.