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Reproductive factors and clinical features of Parkinson's disease

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ABSTRACT

Background: Literature suggests that sex steroid hormones may modify the risk for Parkinson's disease (PD). We investigated the potential effect of reproductive factors on the clinical features of idiopathic PD (IPD) patients.

Methods: All IPD female patients admitted to and evaluated at our Institute over a 12-month period were included in the present cross-sectional study. We investigated the effect of the following parameters by multivariate linear regression analysis: age at menarche, age at menopause, length of fertile life, duration of exposure to endogenous estrogens and cumulative length of pregnancies, use of contraceptives and hormonal replacement therapy.

Results: In total, 579 patients were evaluated and 497 reported menopause before PD onset. In this population, age at PD onset was positively associated with age at menarche and at menopause, length of fertile life and duration of estrogen exposure. Moreover, UPDRS motor score was inversely associated with age at menopause, length of fertile life and duration of estrogen exposure. Increasing age at menarche was also associated with predominant resting tremor at PD onset. In models refitted on patients with early PD (disease duration <5 years; $N = 226$) all the associations found were confirmed. The relationship between surrogates of estrogen exposure and UPDRS motor score actually became more significant.

Conclusions: Our observations support the concept that hormonal exposure of the nigro-striatal network during life may influence its susceptibility to degenerative stimuli in later life, but the association does not seem to be unique? unidirectional. In particular, increased severity of PD signs correlates with shorter duration of estrogen exposure. The underlying mechanisms need to be clarified.

1. Introduction

Regarded mainly as a sporadic disorder of multifactorial origin, Parkinson's disease (PD) is the second most common chronic neurodegenerative disease, which appears to have both genetic and environmental causes [1]. Genetic studies explain no more than 10–30% of cases [1,2] and, although several risk factors have been identified [3–9], the search for etiologic agents is still open. In regard to this issue, previous literature has suggested that reproductive factors may play a role [10–12]. Although evidence from both prospective investigations and case–control studies appears controversial to some extent [10–17], studies have shown that women are less susceptible [18,19] to the disease and develop it later in life [19,20]. Animal-model studies of PD have demonstrated that estrogens possess neuroprotective properties [21,22]. Moreover, a retrospective cross-sectional study [23] and two pilot interventional clinical trials have shown that postmenopausal hormone replacement therapy (HRT) improves motor disability [24,25]. Taken together, these data suggest a beneficial influence of estrogens against the development and progression of PD.

Since knowledge about the presentation of PD symptoms and the related pathophysiologic factors may improve the accuracy and effectiveness of clinical assessment and treatment of the disease, we designed the present study to determine whether reproductive factors contribute to the severity of PD symptoms.

2. Materials and methods

2.1. Data source

We conducted a cross-sectional single-centre study. We used the Parkinson Institute, Milan (Italy) research database, which contains computerized demographic information (age, sex, education, reproductive factors, weight and height and body mass index [calculated as the ratio between weight and height squared –

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kg/m^2]), lifestyle information (smoking status, physical exercise and exposure to environmental/occupational pollutants), general medical information (family history, diagnoses and drug prescriptions) and disease-specific records (disease onset and related features, disease progression and pharmacological therapy) on all patients admitted to the institute for disease assessment. The records of all female patients with a diagnosis of idiopathic Parkinson's disease (IPD) attending the Parkinson Institute for disease assessment between January 2011 and January 2012 were reviewed for this study.

2.2. Subject selection

IPD was diagnosed in agreement with the UK PD Society Brain Bank criteria. Only patients with a confirmed diagnosis of PD and having at least a one-year follow-up were included. Accordingly, from the cohort of patients attending our Institute we excluded case subjects diagnosed with or reporting: multiple system atrophy; progressive supranuclear palsy; cognitive impairment (Mini-Mental State Examination score $<$ 25 points); history of stroke or encephalitis or repeated head injury; presentation of clear signs of vascular parkinsonism; use of anti-dopaminergic drugs ($>$1 month). Patients treated with neurosurgical procedures were also excluded.

2.3. Clinical features

To investigate any potential effect of reproductive factors on clinical presentation we used only data collected at the first visit. Attention was focused on: age at onset (age at which one of the cardinal signs was first noted), levodopa therapy (in mg/day and mg/kg/day; including equivalent dose of other antiparkinsonian medications), clinical rating scales (Hoehn & Yahr and the motor score of the Unified PD Rating Scale [UPDRS; in the "ON" phase]) and symptoms at onset (the first noted). In regard with this last feature, we investigated any effect on the prevalence of resting tremor at diagnosis [20].

2.4. Reproductive factors

Reproductive factors were ascertained by means of a self-administered questionnaire and confirmed through direct interviewing. We collected information on: age at menarche, number and duration of pregnancies, number of miscarriages/abortions, regularity of menses, age at menopause, type of menopause (natural vs. surgical [bilateral oophorectomy]), use of contraceptives and HRT ($>$6 months). Accordingly, the effect of the following parameters was investigated: age at menarche, age at menopause (age at menses cessation for 12 or more continuous months or confirmed by hormone blood level measurements), length of fertile life (defined as the difference between age at menopause and age at menarche), cumulative duration of pregnancies (including miscarriages/abortions), duration of estrogen exposure (defined as the difference between length of fertile life and cumulative duration of pregnancies) and hormonal therapies (hormone-modulating contraceptives and HRT; any use vs. never). In patients who experienced the onset of PD before the menopause we considered the age at disease onset also as the age at menopause.

2.5. Ethics

The study was performed in agreement with the principles of the Declaration of Helsinki and the protocol was approved by the Local Ethics Committee. We obtained written informed consent from every patient recruited.

2.6. Statistical analysis

Categorical variables were presented as counts and percentages and analyzed by Fisher's exact test or the Chi-square test. Continuous variables were reported as means and standard deviation (normal distribution) or medians and inter-quartile range (non-normal distribution; 25th–75th percentile). In respect to these, comparisons between two groups were performed by using Student's *t*-test (normal distribution) or Mann–Whitney *U*-test (non-normal distribution), while comparisons among multiple groups were made by ANOVA (normal distribution) or Kruskal–Wallis test (non-normal distribution). In order to take potential differences in reproductive factors occurring over time into account, patients were stratified according to birth cohort tertiles.

Multivariable linear regression models adjusted for diabetes, hypertension, NSAID use, pollutants exposure, positive family history of PD, previous or current smoking, education, sedentary lifestyle, birth cohort and regular menses were used to evaluate the relationship between reproductive factors (alternative independent variables) and the clinical features of PD (dependent variables). Analysis was adjusted (the inclusion in single models is specified where appropriate) also for: age at onset of PD, disease duration, total daily levodopa equivalent dose (mg/kg) and body mass index. Accordingly, data were presented as coefficient of regression and standard error. Prior to inclusion in the models, collinearity between variables was assessed through Pearson's statistic and variables with a non-normal distribution were transformed on a logarithmic scale.

Two sets of analysis were considered. Primary analysis was based on post-menopausal patients at PD onset because making the end of endogenous estrogen exposure coincide with the onset of PD in patients in whom the onset of PD had occurred before menopause might have introduced bias. Moreover, early-onset PD is more likely to be secondary to other factors (e.g. genetics, exposure to hydrocarbons) [1,26] that could affect the investigation of other variables, such as reproductive factors, acting in later life. Subsequently, sensitivity analysis was performed by refitting the original models on subjects in menopause at PD onset and with disease duration $<$5 years.

All data were analyzed using MEDCALC® for Windows Version 11.3.0.0 (MedCalc Software, Mariakerke, Belgium), setting the level of significance at a two-tailed *P*-value of $<$0.05.

3. Results

The flow chart of the study is reported in Fig. 1. Over a 12-month period 611 female patients with a confirmed clinical diagnosis of IPD were referred to our Institute. Of these 32 were excluded due to incomplete data ($N = 26$) or because they had undergone a neurosurgical procedure ($N = 6$). Onset of PD before menopause occurred in 82 patients (14.2%). Accordingly, the final study population consisted in 497 patients (81.3%). The features of the population at study entry by menopausal status at PD onset are presented in Table 1. In respect to reproductive factors, as expected, patients with onset of PD before menopause were characterized by younger age at menopause, and shorter length of fertile life and duration of estrogen exposure. They also reported younger age at menarche and higher use of contraceptives.

The reproductive characteristics of the population by birth cohort are presented in Table 2. Birth cohort was associated with younger age at menarche, higher use of contraceptives and HRT in

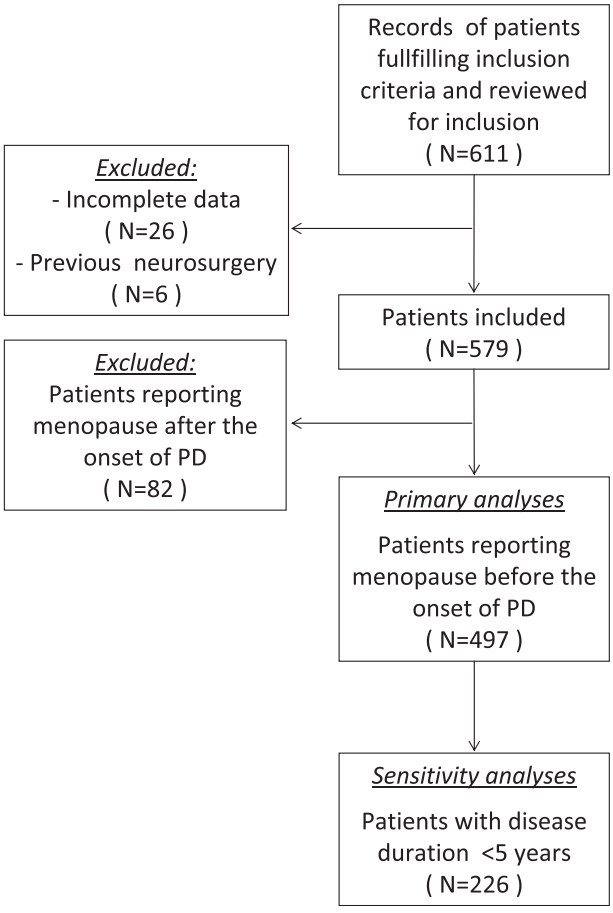

Fig. 1. Study flow chart.