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Reproductive life characteristics in females affected with Parkinson's disease and in healthy control subjects – a comparative study on Polish population

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ABSTRACT

Background: Sex and blood level of sex hormones play a key role not only in the susceptibility to develop Parkinson's disease (PD) but also influence the natural course of the disease. The aim of this study was to compare reproductive lifespan events in females affected with PD and in "non-parkinsonian" age matched subjects and to evaluate whether the whole life endogenous oestrogen level is associated with variables describing the course of the disease.
Materials and methods: Reproductive lifespan, age at menarche, age at menopause, gynaecological interventions and parity were compared in 76 women with idiopathic PD and in the age-adjusted control group of 74 subjects. Affected women underwent neurological and psychological assessment. Data were analysed using Mann–Whitney *U* Test and Spearman Rank Correlation Test.
Results: Women affected with PD had a shorter reproductive lifespan and experienced final menstruation earlier than the control group. Early menopause was reported by 24% of the patients and only by 16% of the control subjects. Parkinsonian women reported more commonly the history of surgical menopause. Duration of reproductive lifespan, age at menopause and the type of menopause influenced both motor and cognitive functioning of patients.
Conclusions: There may be a relationship between the lifetime average endogenous oestrogen level and the susceptibility to develop PD. Longer reproductive lifespan resulting in higher "whole life" female sex steroids concentrations may exert a protective effect on central nervous system, resulting in milder course of the disease.

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1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease that affects 0.15% of the general population. Cases of PD increase steeply with advancing age and are consistently higher in men [1]. These two facts have brought the possible protective meaning of female sex steroids to medical attention. Oestrogens play an extremely important role in human brain development [2]. Female sex hormones may exert their positive effect acting via nuclear and membranous receptors, other neurotransmitters receptors and ion channels [3]. Oestrogens may stimulate neurotrophins synthesis and increase concentrations of antiapoptotic factors [4]. Female sex hormones may also act as antioxidants, which have been proven on human hipoccampal, cultured cells (HT22) [5] and attenuate negative effects of MPTP [6]. It was also proven that oestradiol and oestriol may avert alpha synuclein accumulation as well as destabilize the already formed aggregates [7]. Apart from protective role oestrogens may directly stimulate dopamine synthesis in the striatal cells [8].

Studies on animal models although not unanimous also emphasize the importance of sex hormones for dopaminergic system. The drop of endogenous hormones levels in female monkeys after oophorectomy leads to drop in the number of dopaminergic neurons by about 30% [9]. Sterilized rodents treated with 17-beta oestradiol showed higher levels of dopamine in striatum in comparison to untreated animals [10,11].

The influence of female sex steroids in humans was broadly discussed with regard to cognitive functioning. Higher oestradiol levels were positively correlated with better scores in tests assessing memory and verbal fluency [12,13].

The influence of endogenous oestrogens in women affected with Parkinson's disease is evaluated in vast majority of cases based on analysis of reproductive life events. The studies of Popat et al. [14], Benedetti et al. [15], Yadav et al. [16], Nicoletti et al. [17], and Cereda et al. [18] on age at last menstrual period, type of menopause, cumulative length of pregnancies, use of exogenous oestrogens and its influence on the risk of developing PD brought contradictory results. In some studies it has been noticed that the age at onset of PD was higher with later age at menopause and longer reproductive lifespan [17–20], while the study of Yadav et al. [16] draws attention to cumulative length of pregnancies as a factor delaying the onset of Parkinson's disease. Another large retrospective study involving women, who underwent uni- or bilateral oophorectomy showed that the risk of all types of parkinsonism was two times higher in comparison to control subjects with no history of gynaecological interventions [21]. On the other hand the study of Simon et al. denied any influence of surgical menopause on the incidence of the disease irrespectively of the age of intervention [22].

The purpose of this study was to compare reproductive life events in women affected with Parkinson's disease and in the age adjusted control group. We also wanted to analyse possible correlations between reproductive lifespan events and selected determinants of the natural course of the disease.

2. Materials and methods

Seventy-six females diagnosed with Parkinson's disease treated in the Department of Neurology, of the Medical University of Warsaw and in the outpatients setting were examined. The inclusion criterion in the parkinsonian group was diagnosis of idiopathic Parkinson's disease according to Litvan et al. diagnostic criteria [23]. The exclusion criterion for parkinsonian group was the presence of dementia based on MMSE results as well as the history of surgical interventions (pallidotomy, deep brain stimulation) as the latter could possibly modify the natural course of the disease. The mean age in the PD group was 63 ± 11 years (range 42–82), mean duration of the disease was 8 ± 5 years (range 1–24), and with an average age of onset being 55 ± 12 years. Seventy-four control subjects were randomly selected from the other clinical wards of our hospital. Mean age in the control group was 66 ± 11 years (range 50–89). Only women whose records did not contain any documentation of any form of parkinsonism were included to our study. Cognitively impaired females unable to participate in the interview were excluded from the study. Detailed medical history and the exact record of medications use were not obtained from the patients. Those were meaningless for the analysis of past reproductive life events.

Protocol of the study was accepted by the Bioethical Committee of the Medical University of Warsaw. Informed consent was obtained from all patients.

In both groups of patients we conducted a structured interview that contained:

- Age at menarche.
- Age at final menstrual period.
- Type of menopause (natural vs. surgical), as surgical menopause hysterectomy and oophorectomy were taken together.
- Parity meaning cumulative months of pregnancies.

By subtracting the age at menopause and the age at menarche we calculated the duration of reproductive lifespan.

All patients affected with Parkinson's disease underwent neurological and neuropsychological examination by means of different scales:

- Unified Parkinson's Disease Rating Scale (UPDRS) to determine motor and global functioning of the patient in ON and in OFF stage (after 12 h withdrawal of dopaminergic medication) [24].
- Abnormal Involuntary Movement Scale (AIMS) [25].
- Mini Mental State Examination [26].
- Beck Depression Inventory [27], Parkinson's disease Questionnaire (PDQ39) [28].

We also analysed if any of the reproductive events may influence the determinants of the clinical course of the disease.

Data were analysed with the Mann–Whitney *U* Test for independent group comparisons and the Spearman Rank Correlation Test for the correlation within the assessed results.