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The risk of Parkinson's disease in women who underwent hysterectomy before the age of menopause

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Abstract

Introduction: Parkinson's disease (PD) is the second most common neurodegenerative aging disorder. Oestrogen has been shown to have a neuroprotective effect against PD in animal models.
This study aimed to detect the risk of PD in women who underwent hysterectomy before the age of menopause.
Material and methods: Seventy-six women with PD (study group) were recruited for this retrospective study and compared to 80 controls. Collected data included the education level, smoking, age of menopause, type of menopause (natural or surgical), past surgical history of hysterectomy, type of hysterectomy (hysterectomy only or hysterectomy with oophorectomy [unilateral, bilateral]), and use of postmenopausal oestrogen replacement therapy. The collected data were analysed to detect the risk of PD in women who underwent hysterectomy before the age of menopause.
Results: The odds ratio (OR) and relative risk (RR) of PD was significantly higher after surgical menopause in the study group (30 [39.5%]) compared to controls (17 [21.25%]), (OR 2.4 [95% CI: 1.19–4.8]; p = 0.01, RR 1.9 [95% CI: 1.12–3.1]; p = 0.016). In addition, the OR and RR of PD was significantly higher after bilateral oophorectomy in the study group (19 [25%]) compared to controls (8 [10%]), (OR 3.0 [95% CI: 1.22–7.4]; p = 0.016, RR 2.5 [95% CI: 1.16–5.4]; p = 0.01).
Conclusions: The risk of PD increased in women who underwent hysterectomy and bilateral oophorectomy before the age of menopause, and the risk of PD did not increase whether the menopause, either natural or surgical, occurred before 48 years of age.

Key words: Parkinson's disease, hysterectomy, menopause.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative aging disorder, after Alzheimer's disease. The PD clinical diagnostic criteria include resting tremor, rigidity, bradykinesia, and postural instability [1].

The primary locus of PD is the nigrostriatal pathway comprised of pigmented, dopaminergic neurons within the substantia nigra pars compacta (SNpc), and attendant projections to the putamen [2].

The steady loss of the SNpc dopamine neurons and development of dystrophic striatal projections are hallmarks of PD [3].

PD can be accompanied by autonomic nervous system dysfunction, dementia, depression, and psychosis [4]. In addition to physical disability, PD is associated with an increased likelihood of death [4–6].

Age is the single greatest risk factor for PD, and the rate of PD is expected to increase worldwide (4.1 million in 2005 – 8.7 million by 2030) [7].

The incidence of PD is higher in men than in women, with a ratio of approximately 2:1 [8–11]. Furthermore, women tend to have a later age at onset, fewer symptoms, and better Unified Parkinson's Disease Rating Scale (UPDRS) motor scores when compared with men [11].

Although the exact mechanisms behind the sex differences in PD remain unclear, hormones, in particular oestrogen, have been speculated to be neuroprotective against PD. Oestrogen has been shown to have neuroprotective effect against PD in animal models [12–13].

Moreover, oestrogen was found to modulate nigrostriatal dopaminergic activity [14] through increased dopamine synthesis [15], prevention of Lewy body formation, and α-synuclein aggregation [16]. Oestrogen

can also decrease oxidative stress and protect dopaminergic neurons against apoptosis [15, 17].

Based on these findings; it has been hypothesized that oestrogen could have a protective role against PD in women. However, the results of clinical and epidemiologic studies on the role of oestrogen in PD are conflicting. Therefore, this study was designed to detect the risk of PD in women who underwent hysterectomy (with or without oophorectomy) before the age of menopause.

Material and methods

Seventy-six (76) elderly women (≥ 60 years) with PD (study group) were recruited from the geriatric and gynaecology outpatient department (OPD) and compared to 80 controls in this retrospective study to detect the risk of PD in women who underwent hysterectomy (with or without oophorectomy) before the age of menopause.

This study was conducted over one year (July 2019 – July 2020), and participants were included in this study after informed consents following the Helsinki declaration, and after approval of the study by the department's Ethics Committee (approval number 30_07_20/21).

Women confirmed with PD that started after menopause (either natural or surgical menopause) were included in this study (study group) and were matched with controls of the same age (±2 years) who were free from PD, other parkinsonism, dementia, or psychiatric disorder.

The diagnosis of PD was based on the presence of ≥ 2 cardinal signs (resting tremors, bradykinesia, rigidity, or impaired postural reflexes), in the absence of prominent or early symptoms of more extensive nervous system involvement and/or drug-induced Parkinsonism.

In the study group, inclusion criteria included elderly women (≥ 60 years) with confirmed PD only. Cases of PD with dementia preceding or within the first year of PD motor symptoms and/or drug-induced Parkinsonism were excluded from this study.

Menopause was defined as cessation of menses for ≥ 12 months (end of reproductive ability) [18]. The average age of menopause is 48–51 years [18, 19].

Natural menopause means cessation of menses for ≥ 12 months without any procedure that can cause this menstrual cessation (i.e. medication, surgery, or radiation). Surgical menopause means menopause induced after hysterectomy with or without oophorectomy [18, 19].

The collected data included the education level, smoking, age of menopause, type of menopause (natural or surgical), past surgical history of hysterectomy, type of hysterectomy (hysterectomy only or hysterectomy with oophorectomy [unilateral, bilateral]), and use of postmenopausal oestrogen replacement therapy (ERT). The collected data were analysed to detect the risk of PD in women who underwent hysterectomy before the age of menopause.

Sample size

The required sample size was calculated using G Power software version 3.1.9.4 (Heinrich Heine Universität; Düsseldorf; Germany), setting the α-error probability at 0.05, power (1-β error probability) at 0.95%, and effective sample size (weighted) at 0.3. An effective sample of ≥ 140 women in 2 groups (cases and controls) was needed to produce a statistically acceptable figure.

Statistical analysis

The collected data were statistically analysed using the Statistical Package for Social Sciences (SPSS) version 20 (Chicago, IL, USA). The mean and standard deviation (±SD) were used to present numerical values, while the number (N) and percentage (%) were used to present categorical values. Student's t and the χ^2 test were used for analysis of quantitative and qualitative data, respectively. The odds ratio (OR) and relative risk (RR) of PD in relation to the type of menopause (either natural or surgical) and the type of oophorectomy (either unilateral or bilateral) were also calculated. $P < 0.05$ was considered significant.

Declaration of consent

Participants were included in this study after informed consents following the Helsinki Declaration and after approval of the study by the department's Ethics Committee.

Results

Seventy-six (76) elderly women (≥ 60 years) with PD (study group) were included in this retrospective study and compared to 80 controls to detect the risk of PD in women who underwent hysterectomy (with or without oophorectomy) before the age of menopause.

There was no significant difference between the women with PD (study group) and controls regarding the mean age (73.7 ±5.9 years vs. 73.5 ±5.9 years; $p = 0.4$). The mean age of PD onset in the study group was 68.9 ±6.0 years. The PD onset was between 50 and 59 years in 3.9% (3/76) of the studied women, between 60 and 69 years in 38.2% (29/76), between 70 and 79 years in 46.1% (35/76), and ≥ 80 years in 11.8% (9/76).

There was no significant difference between the study group (with PD) and controls regarding the level of education or smoking habit. There was no signifi-

Table 1. The age, Parkinson's disease onset, education level, smoking, and type of menopause of the studied women compared to controls

Parameters	PD cases (*n* = 76)	Controls (*n* = 80)	*p*-value (95% CI)
Age (years)	73.7 ±5.9	73.5 ±5.9	0.4 (–1.7, 0.2, 2.1)
Mean age of PD onset	68.9 ±6.0		
Age distribution in relation to PD onset, *n* (%)			
50–59 years old	3 (3.9)		
60–69 years old	29 (38.2)		
70–79 years old	35 (46.1)		
≥ 80 years old	9 (11.8)		
Education level, *n* (%)			
Illiterate	10 (13.2)	4 (5)	0.1
Primary school	40 (52.6)	31 (38.75)	0.2
Secondary school or above	26 (34.2)	45 (56.25)	0.08
Smoking, *n* (%)	8 (10.5)	9 (11.25)	1.0
Type of menopause, *n* (%)			
Natural (109)	46 (60.53)	63 (78.25)	0.2
Surgical (47)	30 (39.47)	17 (21.25)	0.06
Hysterectomy without oophorectomy	9 (30)	7 (41.2)	0.5
Hysterectomy with unilateral oophorectomy	2 (6.7)	2 (11.75)	0.5
Hysterectomy with bilateral oophorectomy	19 (63.3)	8 (47.05)	0.5

CI – confidence interval, *N* – number, PD – Parkinson's disease
Data presented as mean and standard deviation (SD) and number and percentage (%).

cant difference between the study group and controls regarding the number of women with natural menopause (60.53% [46/76] vs. 78.25% [63/80], respectively; *p* = 0.2), the number of women with surgical menopause (39.47% [30/76] vs. 21.25% [17/80], respectively; *p* = 0.06) (Table 1).

In addition, there was no significant difference between the study group and controls regarding the number of women who underwent hysterectomy without oophorectomy (30% [9/30] vs. 41.2% [7/17], respectively; *p* = 0.5), hysterectomy with unilateral oophorectomy (6.7% [2/30] vs. 11.75% [2/17], respectively; *p* = 0.5), and hysterectomy with bilateral oophorectomy (63.3% [19/30] vs. 47.05% [8/17], respectively; *p* = 0.5) (Table 1).

The OR and RR of PD was significantly higher after surgical menopause in the study group (30 [39.5%]) compared to controls (17 [21.25%], OR 2.4 [95% CI: 1.19–4.8]; *p* = 0.01, RR 1.9 [95% CI: 1.12–3.1]; *p* = 0.016). In addition, the OR and RR of PD was significantly higher after bilateral oophorectomy in the study group (19 [25%]) compared to controls (8 [10%]), (OR 3.0 [95% CI: 1.22–7.4]; *p* = 0.016, RR 2.5 [95% CI: 1.16–5.4]; *p* = 0.01) (Table 2).

The OR and RR of PD was statistically insignificant after hysterectomy without oophorectomy (9 [11.8%] in the study group vs. 7 [8.75%] in controls, [OR 1.4; *p* = 0.5], [RR 1.4; *p* = 0.5]), or after hysterectomy and unilateral oophorectomy (2 [2.6%] in the study group

vs. 2 [2.5%] in controls, [OR 1.05; *p* = 0.9], [RR 1.05; *p* = 0.9]). The OR and RR was statistically insignificant when the natural menopause occurred before 48 years (3 [3.9%] in the study group vs. 2 [2.50%] in controls, [OR 2.1; *p* = 0.4], [RR 2.05; *p* = 0.4]) or when the surgical menopause occurred before 48 years (16 [21.05%] in the study group vs. 9 [11.25%] in controls, [OR 1.2; *p* = 0.7], [RR 1.1; *p* = 0.7]). The use of ERT (either for < or ≥ 12 months) did not increase the OR or RR of PD in the 2 studied groups (Table 2).

Discussion

Oestrogen has been shown to have a neuroprotective effect against PD in animal models [13, 20]. Oestrogen was found to modulate nigrostriatal dopaminergic activity [14] through increased dopamine synthesis [15]. Oestrogen can also decrease oxidative stress and protect dopaminergic neurons against apoptosis [15]. Oestrogen could play a protective role against PD in women.

Therefore, 76 women with PD (study group) were included in this retrospective study and compared to 80 controls, to detect the risk of PD in women who underwent hysterectomy before the age of menopause.

The OR and RR of PD was significantly higher after surgical menopause in the study group (30 [39.5%]) compared to controls (17 [21.25%]),

Table 2. The odds ratio and relative risk of Parkinson's disease in relation to type of menopause, type of oophorectomy, and hormonal replacement therapy

Parameters	PD cases, n = 76 (%)	Controls, n = 80 (%)	p-value OR (95% CI)	p-value RR (95% CI)
Menopause type (total 156)				
Natural (109)	46 (60.5)	63 (78.75)	0.01*	0.016*
Surgical (47)	30 (39.5)	17 (21.25)	2.4 (1.19–4.8)	1.9 (1.12–3.1)
Hysterectomy without oophorectomy (total 156)				
No (140)	67 (88.2)	73 (91.25)	0.5	0.5
Yes (16)	9 (11.8)	7 (8.75)	1.4 (0.49–3.97)	1.4 (0.53–3.5)
Hysterectomy with unilateral oophorectomy (total 156)				
No (152)	74 (97.4)	78 (97.5)	0.9	0.9
Yes (4)	2 (2.6)	2 (2.5)	1.05 (0.14–7.7)	1.05 (0.15–7.3)
Hysterectomy with bilateral oophorectomy (total 156)				
No (129)	57 (75)	72 (90)	0.016*	0.01*
Yes (27)	19 (25)	8 (10)	3.0 (1.22–7.4)	2.5 (1.16–5.4)
Age of menopause (total 156))				
≥ 48 years (126)	59 (77.6)	67 (83.7)	0.3	0.3
< 48 years (30)	17 (22.4)	13 (16.3)	1.4 (0.3–1.5)	1.4 (0.72–2.6)
Age of natural menopause (total 109)				
≥ 48 years (104)	43 (56.6)	61 (76.25)	0.4	0.4
< 48 years (5)	3 (3.9)	2 (2.50)	2.1 (0.34–13.3)	2.05 (0.36–11.8)
Age of surgical menopause (total 47)				
≥ 48 years (22)	13 (17.1)	9 (11.25)	0.7	0.7
< 48 years (25)	16 (21.05)	9 (11.25)	1.2 (0.38–4.0)	1.1 (0.63–1.9)
Postmenopausal use of HRT (total 156)				
≥ 12 months (135)	67 (88.2)	68 (85.0)	0.6	0.5
< 12 months (21)	9 (11.8)	12 (15.0)	0.76 (0.30–1.93)	0.79 (0.35–1.8)

CI – confidence interval, HRT – hormonal replacement therapy, N – number, OR – odds ratio, PD – Parkinson's disease, RR – relative risk
* significant difference
Data presented as number and percentage (%).

(OR 2.4 [95% CI: 1.19–4.8]; p = 0.01, RR 1.9 [95% CI: 1.12–3.1]; p = 0.016). In addition, the OR and RR of PD was significantly higher after bilateral oophorectomy in the study group (19 [25%]) compared to controls (8 [10%]), (OR 3.0 [95% CI: 1.22–7.4]; p = 0.016, RR 2.5 [95% CI: 1.16–5.4]; p = 0.01).

The increased odds and risk of PD in women who underwent bilateral oophorectomy before the age of menopause support the protective role of oestrogen against PD.

One mechanism can explain this finding: the hormonal changes occurring after bilateral oophorectomy before the age of menopause differ from those occurring during natural menopause or after bilateral oophorectomy in menopausal women. Bilateral oophorectomy before the age of menopause causes a sudden decline of oestrogen as well as progesterone with sudden disruption of the hypothalamic-pituitary-ovarian axis [21].

Several clinical studies showed the protective effect of oestrogen against PD in animal models. Callier *et al.* concluded that oestradiol (17-β and 17-α) in a mouse model protects striatal dopaminergic neurons against neurotoxins [22].

Datla *et al.* found that the loss of dopaminergic neurons in the substantia nigra was greater in animal model with low oestrogen [23].

Gao *et al.* suggested a neuroprotective action of oestrogen against methamphetamine-induced nigrostriatal dopaminergic neurotoxicity [24]. Gajjar *et al.* concluded that oestrogen may exert a rapid neuroprotective effect in mice [25].

Leranth *et al.* observed an essential role of oestrogen to maintain the integrity of the nigral dopamine system in primates, and they suggested ERT as a new treatment strategy for PD [26].

In addition, several clinical studies showed the protective effect of oestrogen against PD in women. Benedetti *et al.*, in spite of their small sample size, concluded that there is an increased risk of PD in conditions causing an early reduction of endogenous oestrogen [19].

Saunders-Pullman *et al.* found a positive association between oestrogen use and decreased severity

of early PD, which suggests a beneficial effect of ERT in early PD [27].

Currie *et al.* also concluded that the postmenopausal ERT may be associated with reduced risk of PD [28].

The association between oophorectomy and increased risk of PD may also be explained by genetic susceptibility that increases the risk of both outcomes independently [29–30].

The OR and RR were statistically insignificant when the natural menopause occurred before 48 years (3 [3.9%] in the study group vs. 2 [2.50%] in controls, [OR 2.1; *p* = 0.4], [RR 2.05; *p* = 0.4]) or when the surgical menopause occurred before 48 years (16 [21.05%] in the study group vs. 9 [11.25%] in controls, [OR 1.2; *p* = 0.7], [RR 1.1; *p* = 0.7]).

Similarly, Liu *et al.* conducted a large prospective study including 119,166 postmenopausal women and found that the risk of PD was not significantly associated with age of menarche and/or age of menopause [31].

In addition, Ragonese *et al.* found that the risk of PD was significantly associated with short fertile-life length (< 36 years) [32].

Although, Currie *et al.* concluded that the postmenopausal ERT may be associated with reduced risk of PD. The use of ERT (either for < or ≥ 12 months) in this study does not increase the OR, or RR of PD in the 2 studied groups [28].

Liu *et al.* also found no association between risk of PD and hormonal therapy use (either past or current use) ≥ 5 years [31]. Moreover, Yoo *et al.* found that the use of hormonal replacement therapy (HRT) increases the risk of PD by 17% [33].

A similar neuroprotective effect of oestrogen against dementia and cognitive functions has been proposed. Rocca *et al.* observed an increased risk of cognitive impairment or dementia in women who underwent oophorectomy before the age of menopause [34].

In addition, Marder *et al.* found that the ERT was protective against development of dementia within the setting of PD, when PD dementia participants were compared to controls, but it did not affect the risk of PD [35].

The conflicting results regarding the association between PD and ERT or HRT should be confirmed in larger studies.

This study was the first comparative study conducted in our region to detect the risk of PD in women who underwent hysterectomy before the age of menopause.

This study found that the risk of PD increased in women who underwent hysterectomy and bilateral oophorectomy before the age of menopause, but did not increase in women who underwent hysterectomy and unilateral oophorectomy before the age of menopause. This study also found that the risk of PD did not increase when the menopause (natural or surgical) occurred before 48 years of age or with the use of ERT.

This study concluded that the risk of PD increased in women who underwent hysterectomy and bilateral oophorectomy before the age of menopause. This study also concluded that the risk of PD did not increase when the menopause, either natural or surgical, occurred before 48 years of age or with the use of ERT.

Women who refused to participate and retrospective design were the limitations of this study. Larger future studies are needed to confirm the association between PD and ERT or HRT.

Conclusions

The risk of PD increased in women who underwent hysterectomy and bilateral oophorectomy before the age of menopause, and the risk of PD did not increase when the menopause, either natural or surgical, occurred before 48 years of age.

Disclosure

The authors report no conflict of interests.

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