Frequency of Total Abdominal Hysterectomy-Bilateral Salpingo-Oophorectomy (TAH-BSO) History in Women with Parkinson's Disease

Parkinson Hastalığı olan Kadınlarda Total Abdominal Histerektomi -Bilateral Salpingo-Ooferektomi (TAH-BSO) Sıklığı

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ABSTRACT

Objective: Estrogen is thought to play a protective role in a predisposition to the Parkinson's disease (PD). It was aimed to investigate the frequency of total abdominal hysterectomy-bilateral salpingo-oophorectomy (TAH-BSO) history causing withdrawal estrogen in women with PD in this study.

Methods: The electronic records of the Movement Disorders Unit of the Neurology Department were reviewed. Female with PD were selected and compared with age-matched controls without movement disorders. The patients were divided into two groups (<45 years and ≥45 years) according to their age at TAH-BSO to investigate the effect of premature estrogen withdrawal. Characteristics of PD were evaluated in these groups.

Results: Total 675 patients and 125 controls were included. The frequency of TAH-BSO was found higher in patients (15.3%) than controls (12%) but it was not significantly (p=0.34). Age of symptom onset, disease severity and daily levodopa dose were not different in patients (n=30) with age at TAH-BSO <45 years compared with the patients (n=73) with those ≥45 years at TAH-BSO. Risk of PD was found to be slightly increased in patients aged <40 years at the time of surgery (OR=1.94, 95% CI: 0.19-19.59, p=0.57) compared with those aged 40-44 years (OR=0.39, 95% CI: 0.10-1.49, p=0.17) and >45 years (OR=1.58, 95% CI: 0.32-7.80, p=0.57).

Conclusion: The frequency of TAH-BSO history in women with PD is not different compared to the control group. Risk of PD may slightly increased in patients aged <40 years of TAH-BSO. Age of TAH-BSO did not affect the analyzed clinical parameters of PD.

Key Words: Parkinson's disease; woman; menopause; estrogen, surgery

ÖZET

Amaç: Östrojenin Parkinson hastalığı (PH) için koruyucu bir rol oynadığı düşünülmektedir. Bu çalışmada östrojen çekilmesine neden olan Total Abdominal Histerektomi-Bilateral Salpingo-ooferektomi (TAH-BSO) sıklığının Parkinson hastalığı olan kadınlarda araştırılması amaçlandı.

Yöntem: Bu çalışmada Nöroloji Bölümü'nün, Hareket Bozuklukları Ünitesine ait elektronik kayıtları retrospektif olarak değerlendirildi. Parkinson tanısı olan kadın hastalar seçildi ve yaş uyumlu, herhangi bir hareket bozukluğu olmayan kontroller ile karşılaştırıldı. Parkinson hastalarında, prematür östrojen çekilmesinin etkisini araştırmak için TAH-BSO uygulanma yaşına göre 2 gruba ayrıldı (45 yaş altı ve 45 yaş üstü). Bu iki grubun klinik özellikleri karşılaştırıldı.

Bulgular: Çalışmaya 675 Parkinson hastası ile 125 kontrol dahil edildi. TAH-BSO sıklığı, Parkinson hastalarında (%15,3) kontrollerden (%12) daha yüksek bulundu ancak istatistiksel olarak anlamlı değildi (p=0,34). Kırkbeş yaş altında TAH-BSO hikayesi olan Parkinson hastaları (n=30), 45 yaş üstü TAH-BSO olan Parkinson hastaları (n=73) ile karşılaştırıldığında semptom başlangıç yaşı, hastalık şiddeti ve günlük levodopa dozu açısından farklılık gözlenmedi. Kırk yaş altında TAH-BSO cerrahi öyküsü olan kadın Parkinson hastalarında hastalık riski (OR=1,94 95% CI: 0,19-19,59 p=0,57) 40-44 yaş arası TAH-BSO hikayesi olanlar (OR=0,39 95% CI: 0,10-1,49 p=0,17) ve 45 yaş üstü TAH-BSO hikayesi olanlar ile karşılaştırıldığında (OR=1,58 95% CI: 0,32-7,80 p=0,57) hafif artmış bulundu.

Sonuç: Parkinson hastalığı olan kadınlarda TAH-BSO öyküsü sıklığı kontrol grubu ile karşılaştırıldığında farklı değildir. Bu cerrahiyi 40 yaş altında olan kadınlarda Parkinson hastalığı riski hafif de olsa artabilir. Ayrıca TAH-BSO, PH'nın analiz edilen klinik özelliklerini etkilememiştir.

Anahtar Sözcükler: Parkinson hastalığı, kadın, menapoz, östrojen, cerrahi

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INTRODUCTION

Parkinson's disease (PD) is one of the most common movement disorders. Disease prevalence varies due to different methodologies in epidemiologic studies, but acceptable prevalence ranges from 1 to 2 in 1000 in populations. The incidence rates of PD are estimated to range between 8 and 18 per 100 000 person-years. Incidence increases with aging (1,2).

Age is the most important risk factor known for the PD. Furthermore, genetic and some environmental risk factors have been identified in the etiology of PD. In the presence of PD in first-degree family members, the risk of disease increases by 2 to 3 times. Environmental risk factors are defined as diet, certain pesticides, head trauma, alcohol, rural living, and toxic levels of manganese or carbon monoxide (3,4). Male sex is another risk factor for PD, which affects men more than women. The disease affects men 1.5 times more often than women (5,6). The best known reason for the sex difference in PD is estrogen. It is thought that the estrogen in women is a protective factor against the disease and the risk of disease may increase with surgical or natural menopause (7).

Menopause can be surgically induced through oophorectomy and also bilateral salpingo-oophorectomy during hysterectomy for some pathologies is a common surgery procedure in premenopausal women. Surgical menopause, which causes withdrawal of estrogen, may have more severe consequences than natural menopause such as an increased risk of PD (8). It was aimed to investigate the frequency of TAH-BSO history in women with PD and compare with controls in this study.

METHODS

This retrospective study made use of the electronic medical records of the Movement Disorders Unit of the Department of Neurology, University of Ankara, between December 2006 and December 2018. The records were reviewed by a neurologist and a movement disorder specialist.

Patients

All female patients with idiopathic PD based on the United Kingdom International Brain Bank criteria, and with a known levodopa response were included in the study (9). Patients with conditions such as hydrocephalus, brain tumor, recurrent head trauma, and long-term neuroleptic use prior to the onset of PD, and those with a sudden onset of disease symptoms or gradual progression, with no levodopa response and with Parkinson-Plus syndromes were excluded from the study. Age, Hoehn and Yahr (HY) scale, and the daily levodopa equivalent dose (LED) in the first visit, age of symptom onset, TAH-BSO history, and age of TAH-BSO were recorded for patients. The presence or absence of TAH-BSO history was obtained from the history given by the patient (or a family member), on which the patient provided information about past surgical procedures. The presence of bilateral oophorectomy was also considered as being the cause of surgical menopause. Considering the age at the time of TAH-BSO surgery, the population was divided into two groups for advanced studies, taking the early withdrawal of estrogen into consideration (<45 years and ≥45 years) (10).

Controls

Patients who were referred with a preliminary diagnosis of parkinsonism, but were found not to have PD, tremors or any movement disorder, and with a full medical record and in a similar age range as the patient group were selected randomly to serve as the control group. The controls were evaluated retrospectively over a fixed period of time by a movement disorder specialist. Other neurologic clinical conditions such as stroke, epilepsy, dementia, depression, polyneuropathy, ataxia, and neuromuscular junction disease were excluded.

Statistical analysis

Descriptive statistics are expressed as mean±standard deviation, frequency distribution, and percentage. The distribution of data was analyzed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Independent samples with normal distribution were evaluated using a t-test. Nonparametric data were analyzed using the Mann-Whitney U test. Categorical variables were analyzed using the Chi-square test and Fisher's exact test. Odds ratios (OR) were calculated using regression analysis (corrected for age). $P<0.05$ was accepted as being statistically significant. The Windows SPSS (IBM SPSS Statistics for Windows, Version 21.0, IBM Corp, Armonk, NY, USA) software package was used for the statistical analyses.

RESULTS

The medical records of 827 female patients selected from among the 2147 files of patients with parkinsonism between December 2006 and December 2018 were evaluated. A total of 675 women with idiopathic PD were included in the study. A total of 125 individuals in the same age range as the patients were included in the study and randomly selected to from the control group.

The characteristics of study groups are presented in Table 1. One hundred three (15.3%) patients with PD and 15 (12%) controls had a history of TAH-BSO. The frequency of TAH-BSO history was not different between the groups and the mean age at TAH-BSO was similar between patient and control (49.75±10.13 years and 47.80±7.89 years, p=0.42).

Table 1. Characteristics of patient and control

	Patient (n=675)	Control (n=125)	p
Age, years	64.58 (10.01)	64.02 (8.43)	0.15
Age of symptom onset, years	58.4 (11.2)	-	-
LED, mg	589 (534)	-	-
HY scale	2.1 (median:2)	-	-
TAH-BSO, n (%)	103 (15.3)	15 (12)	0.34
Age of TAH-BSO, years	49.75 (10.13)	47.8 (7.8)	0.36
Interval between TAH-BSO and symptom onset, years	10.9 (median:10)	-	-

Data are shown as mean (± SD)
TAH-BSO: Total Abdominal Hysterectomy-Bilateral Salpingo-oophorectomy, LED: levodopa equivalent dose, HY: Hoehn andYahr

The number of patients with an age at TAH-BSO of <45 years was 30 (4.4%) and patients with an age at TAH-BSO ≥45 years was 73 (10.8%). In the control group, the number of subjects an age with TAH-BSO<45 was 7 (5.6%) and ≥45 years was 8 (6.4%). No statistically significant differences were found between the groups (p=0.23). Among the patients with PD, age of symptom onset, severity of disease according to the HY scale, and LED were similar in the two PD groups according to TAH-BSO age <45 years and ≥45 years (p=0.42, p=0.06, p=0.22) (Table 2).

Table 2. Disease characteristics of Parkinson patients with TAH-BSO

Data	Patients with age of TAH-BSO < 45 years	Patients with age of TAH-BSO ≥45 years	p
Age of symptom onset	59.34 (10.29)	61.41 (9.52)	0.42
HY scale, median	2.33	2.02	0.06
LED, mg	486.28 (613)	670.73 (641)	0.22

Data are shown as mean (± SD)
TAH-BSO: Total Abdominal Hysterectomy-Bilateral Salpingo-oophorectomy, HY: Hoehn andYahr, LED: levodopa equivalent dose,

TAH-BSO did not have a significant relationship with the disease risk when the Parkinson's patients compared the controls (OR=0.889, 95% CI=0.64-1.2, p=0.46). Parkinson patients with TAH-BSO history after 50 years of age did not have a significant risk increase. Risk was found to be slightly increased in patients with PD with an age at the time of surgery <40 years (OR=1.94, 95% CI: 0.19-19.59, p=0.57) (Table 3).

Table 3. Relationship between the PD risk and age of TAH-BSO

Age of TAH-BSO	OR[a]	95% CI	p
<40	1.94	0.19-19.59	0.57
40-44	0.39	0.10-1.49	0.17
45-49	1.58	0.32-7.80	0.57
≥50	Reference		

CI, confidence interval; OR, odds ratio; PD, Parkinson disease, TAH-BSO: Total Abdominal Hysterectomy-Bilateral Salpingo-oophorectomy
[a] Adjusted age and smoking p<0.05

DISCUSSION

The association between estrogen and PD is still unknown, and a lack of consensus remains (11). Menopause (withdrawal of estrogen), whether surgical or natural, may increase risk of PD according to observational studies (12). However, the frequency of TAH-BSO history was found similar in patients with PD and controls in this large case-control study. The frequency of surgical menopause for Parkinson patients is variable in retrospective studies. Benedetti et al. have investigated frequency of hysterectomy (without bilateral oophorectomy) and found a higher in total 72 patients with PD than the controls (8). In another small case-control study investigating the reproductive factors and the risk of PD in women, rate of surgical menopause was reported high in the patients by Nitkowska et al. In contrast, Ragonese et al. have found the rates of surgical menopause higher in the control group. (13,14).

Surgical menopause, induced through bilateral oophorectomy, occurs before the natural menopause, and results in the early cessation of female sex hormone exposure. Therefore, bilateral oophorectomy is frequently preferred at a more advanced age, rather than unilateral oophorectomy. A hysterectomy combined with a bilateral oophorectomy results in a surgical menopause in more than 10% of women (15,16). Accordingly, the control group comprised women of a similar age to the patient group. The mean age at TAH-BOS was around 50 years, and it was similar in both groups. In addition to cases with TAH-BSO, those with bilateral oophorectomy alone were also included in the present study. Bilateral oophorectomy was performed due to malignancy in two control cases at <40 years of age.

The aim of including an elective oophorectomy in patients undergoing hysterectomy is to prevent ovarian malignancy, although it may increase the risk of cardiovascular disease, dementia, PD, and anxiety and depression when performed at <45 years of age (17). In the present study, the number of patients with a prior TAH-BSO performed at <45 years of age was similar and low in both groups. TAH-BSO performed under or above the age of 45 years in the group of patient with PD was found to have no effect on the age of symptom onset, disease severity, and LED.

The impact of surgical menopause on the risk of PD is controversial. Surgical menopause may be productive when compared with natural menopause. On the other hand, the risk of PD may increase if the age at surgery is under the 40 years (18-20). Similarly, in the present study, a slightly increased risk was detected in those who underwent TAH-BSO at age <40 years. The expected average age of menopause is 51 years, but it is seen at variable rates between the ages of 40 and 60 years. Menopause under the age of 40 years is considered premature menopause (21,22). Premature menopause in women and the earlier cessation of estrogen exposure seems to constitute a risk factor for PD, and the increased risk of disease in patients who underwent TAH-BSO at <40 years may also be attributed to this.

The main limitations of the present study include the fact that other reproductive factors, such as age at menarche, oral contraceptive use, age at natural menopause and postmenopausal hormone use, which all play role in life-long estrogen exposure and may affect the risk of PD in the patient group, were unknown, as well as the selection of the control group.

In summary, the frequency of TAH-BSO history in female patients with PD is not significantly different when compared with those without PD. Risk of disease may be slightly increased when the age at surgery is <40 years. In addition, the association between estrogen and the risk of PD is also as yet unclear; therefore, future studies are required.

Conflict of interest
No conflict of interest was declared by the authors.

REFERENCES

1. Von Campenhausen S, Bornschein B, Wick R, Bötzel K, Sampaio C, Poewe W, et al. Prevalence and incidence of Parkinson's disease in Europe. Eur Neuropsychopharmacol 2005;15(4):473–490.
2. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. Lancet Neurol. 2016;15(12):1257-1272.
3. Savica R, Grossardt BR, Bower JH, Ahlskog JE, Rocca WE. Risk factors for Parkinson's disease may differ in men and women: an exploratory study. Horm Behav. 2013;63(2):308-314.
4. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. J Neural Transm (Vienna). 2017;124(8):901-905.
5. Van Den Eeden SK, Tanner CM, Bernstein Al, Fross RD, Leimpeter A, Bloch DA, et al. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. Am J Epidemiol. 2003;157:1015–1022.
6. Picillo M, Nicoletti A, Fetoni V, Garavaglia B, Barone P, Pellecchia MT. The relevance of gender in Parkinson's disease: a review. J Neurol. 2017;264(8):1583-1607.
7. Liu B, Dluzen DE. Oestrogen and nigrostriatal dopaminergic neurodegeneration: animal models and clinical reports of Parkinson's disease. Clin Exp Pharmacol Physiol. 2007;34(7):555-565.
8. Benedetti MD, Maraganore DM, Bower JH, McDonnell SK, Peterson BJ, Ahlskog JE, et al. Hysterectomy, menopause, and estrogen use preceding Parkinson's disease: an exploratory case-control study. Mov Disord 2001;16:830–837.
9. Litvan I, Bhatia KP, Burn DJ, Goetz CG, Lang AE, McKeith I, et al. Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. Mov Disord 2003;18:467–486
10. North American Menopause Society. Menopause Practice: A Clinician's Guide. 3rd ed. Cleveland, OH: North American Menopause Society; 2007.

11. Simon KC, Chen H, Gao X, Schwarzschild MA, Ascherio A. Reproductive factors, exogenous estrogen use, and risk of Parkinson's disease. Mov Disord. 2009 15;24(9):1359-1365.

12. Marras C, Saunders-PR. The Complexities of Hormonal Influences and Risk of Parkinson's Disease. Mov Disord. 2014; 29(7): 845–848.

13. Nitkowska M, Czyżyk M, Friedman A. Reproductive life characteristics in females affected with Parkinson's disease and in healthy control subjects - a comparative study on Polish population. Neurol Neurochir Pol. 2014;48(5):322-327.

14. Ragonese P, D'Amelio M, Salemi G, Aridon P, Gammino M, Epifano A, et al. Risk of Parkinson disease in women: effect of reproductive characteristics. Neurology 2004;62(11):2010–2014.

15. Redburn JC, Murphy MF. Hysterectomy prevalence and adjusted cervical and uterine cancer rates in England and Wales. BJOG 2001;108:388–395.

16. Phung, TK, Waltoft BL, Laursen TM, Settnes A, Kessing LV, Mortensen PB, et al. Hysterectomy, oophorectomy and risk of dementia: a nationwide historical cohort study. Dement Geriatr Cogn Disord. 2010;30(1):43-50.

17. Evans EC, Matteson KA, Orejuela FJ, Alperin M, Balk EM, Sherif E-N, et al. Society of Gynecologic Surgeons Systematic Review Group. Salpingo-oophorectomy at the Time of Benign Hysterectomy: A Systematic Review. Obstet Gynecol. 2016;128(3):476-485.

18. Lv M, Zhang Y, Chen GC, Li G, Rui Y, Qin L, et al. Reproductive factors and risk of Parkinson's disease in women: A meta-analysis of observational studies. Behav Brain Res. 2017;335:103-110.

19. Noyce AJ, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Giovannoni G, Lees AJ, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. Ann Neurol. 2012;72(6):893-901.

20. Liu R, Baird D, Park Y, Freedman ND, Huang X, Hollenbeck A, et al. Female reproductive factors, menopausal hormone use, and Parkinson's disease. Mov Disord. 2014;29(7):889-896.

21. Emre SY, Balik KI, Bauthan O. Ovarian aging and premature ovarian failure. J Turk Ger Gynecol Assoc. 2014;15:190–196.

22. Fenton AJ. Premature ovarian insufficiency: Pathogenesis and management. J Midlife Health. 2015;6:147–153.