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Lifetime Exposure to Estrogen and Progressive Supranuclear Palsy: ENGINE-PSP study

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SUPPLEMENTARY DATA

Additional supplementary table and figure are found in the online version of this article at the publisher's web-site.

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Abstract

BACKGROUND—Studies suggesting a protective effect of estrogen in neurodegenerative diseases prompted us to investigate this relationship in progressive supranuclear palsy (PSP).

METHODS—This case-control study evaluated the self-reported reproductive characteristics and estrogen of 150 women with PSP and 150 age -matched female controls who participated in the Environmental Genetic-PSP study. Conditional logistic regression models were generated to examine associations of PSP with estrogen.

RESULTS—There was no association between years of estrogen exposure duration and PSP. There was a suggestion of an inverse association between composite estrogen score and PSP that did not reach statistical significance ($P = 0.06$). Any exposure to estrogen replacement therapy halved the risk of PSP (odds ratio = 0.52; 95% confidence interval = 0.30-0.92; $P = 0.03$). Among PSP cases, earlier age at menarche was associated with better performance on Hoehn and Yahr (H&Y) stage ($\beta = -0.60$; SE = 0.26; $P = 0.02$) and Unified Parkinson's Disease Rating Scale (UPDRS) II score ($\beta = -5.19$; SE = 2.48; $P = 0.04$) at clinical examination.

CONCLUSIONS—This case-control study suggests a protective role of lifetime estrogen exposure in PSP. Future studies will be needed to confirm this association.

Keywords

Progressive supranuclear palsy; Parkinsonism; Estrogen; Estrogen replacement therapy; Case-control study

INTRODUCTION

Studies conducted in experimental models of neurodegenerative diseases have suggested neuroprotective effects of estrogens.¹ Although a higher incidence of Parkinson's disease (PD)^{2, 3} in men than in women and a higher risk of developing Alzheimer's dementia (AD)⁴ in postmenopausal women than in age-matched men have been presumed to be associated with neuroprotective effects of estrogen, epidemiologic studies of PD⁵⁻⁸ and AD^{9, 10} do not provide consistent evidence for a protective role for estrogen. To our knowledge, the role of estrogen in progressive supranuclear palsy (PSP), a primary tauopathy, has not been investigated. Thus, we examined the association between estrogen, PSP, and PSP disease severity in the multicenter case-control risk factor study, Environmental and Genetic PSP (ENGINE-PSP).

METHODS

Study population

The ENGINE-PSP study enrolled 350 incident PSP cases and 300 controls from fifteen sites across North America.¹¹ PSP was defined using the National Institute of Neurological Disorders and Stroke-Society for PSP (NINDS-SPSP) criteria.¹² Cases were requested to identify age (± 5 years) and sex-matched non-blood relatives as controls. Cases were excluded from this parent study if they scored < 24 on the Mini-Mental State Examination (MMSE)¹³ and controls were excluded if they scored < 28 on the Telephone Interview of Cognitive Status (TICS)¹⁴ or scored ≥ 4 on the Telephone Questionnaire for PD.¹⁵ The 300 matched pairs were 50% male and 50% female. The analysis included 150 women with PSP and 150 age-matched control women (see supplementary figure). This study was approved by the institutional review boards of all participating sites. All study subjects provided written informed consent prior to participating in the study.

Study Procedures

The modified version of the Stewart telephone questionnaire¹⁶ was administered to participants to collect demographic and reproductive characteristics. Participants were asked about exposures to endogenous estrogen: ages at menarche and last menstrual cycle; and exposures to exogenous estrogen: oral contraceptive use (ever/never), duration of oral contraceptive use (years), estrogen replacement therapy (ERT) use for a period of at least 6 months (ever/never), duration of ERT use (years), and if they previously had a hysterectomy and/or oophorectomy.

To determine disease severity, the PSP Rating Scale (PSPRS),¹⁷ Unified Parkinson Disease Rating Scale (UPDRS; I, Mentation; II, Activities of daily living; III, Motor examination),¹⁸ modified Hoehn and Yahr stage (H&Y),¹⁹ MMSE,¹³ Mattis Dementia Rating Scale-2 (MDRS-2),²⁰ California Verbal Learning Test 2nd edition (CVLT-II), and Frontal Assessment Battery (FAB)²¹ were administered to all PSP cases. Controls were administered the TICS¹⁴ and Telephone Questionnaire for PD.¹⁵ The questionnaires were administered one to four weeks after the cases' evaluations, depending on participant availability. The subjects were recruited between October 1st, 2006 and February 1st, 2013.

Statistical analysis

Demographic and reproductive characteristics in cases and controls were compared using t-tests and chi-square tests. Age at menopause was estimated using age at last menstrual cycle or age at oophorectomy.⁶ Only women who reported taking systemic ERT were classified as using exogenous estrogen. Lifetime exposure to estrogen (estrogen length) was the sum of the difference between age at menopause and menarche (reproductive period) and years of ERT use (Fig. 1).²² To account for additional indicators of lifetime estrogen exposures, we generated a composite estrogen score.²³ The composite estrogen score was the sum of the positive responses to the following four additional exposures to estrogen: early age at menarche (< 10.5 years; yes/no), history of hysterectomy or oophorectomy (yes/no), use of ERT (yes/no), and late age at menopause (> 53 years for women with no prior surgery and > 46 years for women who had a previous bilateral oophorectomy; yes/no). Contribution of

each component toward the score was evaluated to ensure that one variable was not driving an observed association.

Conditional logistic regression models were generated to determine if there was an association between reproductive characteristics and PSP. Odds ratios (OR) and 95% confidence intervals (CI) were estimated after adjusting for race/ethnicity, education, and smoking duration. These covariates were selected a priori as potential confounders.^{8, 24, 25}

To determine the association between estrogen and PSP disease severity, linear regression models were fit after adjusting for race/ethnicity, education, smoking duration, and disease duration.

RESULTS

Baseline demographics of PSP cases and controls are shown in supplementary table 1. The mean age of participants was 68.7 ± 6.5 years. Ninety-three percent of PSP cases and 98% of controls identified themselves as white ($P = 0.05$). Controls were more educated than cases ($P = 0.003$). PSP cases and controls reported 10.4 ± 19.0 and 6.6 ± 15.5 smoking pack-years, respectively ($P = 0.04$). Race/ethnicity, education, and smoking duration were adjusted for in all models. Forty percent of women reported a previous hysterectomy and/or oophorectomy. ERT was reported by significantly more controls than cases ($P = 0.009$) (Table 1). Although there was no association between estrogen exposure duration and PSP (OR = 1.02; 95% CI = 0.96-1.09; $P = 0.51$), there was a suggestion of inverse association between composite estrogen score and PSP that did not reach statistical significance ($P = 0.06$). Compared to women with the lowest overall exposure to estrogen (score 0), women with higher levels of cumulative estrogen had a decreased risk of PSP (score 1, OR = 0.51; 95% CI = 0.24-1.09, score 2, OR = 0.46; 95% CI = 0.22-0.98, score 3 + 4, OR = 0.49, 95% CI = 0.19-1.011, P -trend = 0.06). Additionally, we found an association between using ERT and decreased risk of PSP (OR = 0.52; 95% CI = 0.30-0.92; $P = 0.03$). There were no associations between endogenous estrogens or oral contraceptive use and PSP. (Table 1).

All PSP cases were evaluated for disease severity (see supplementary table). Although a longer estrogen length was significantly associated with improved CVLT-II cued recall score, the improvement per year increase was clinically minimal ($\beta = 0.08$; standard error (SE) = 0.04; $P = 0.04$). Early age at menarche was associated with less severe H&Y stage ($\beta = -0.60$; SE = 0.26; $P = 0.02$) and UPDRS II ($\beta = -5.19$; SE = 2.48; $P = 0.04$). There were no other significant associations between estrogen exposures and disease severity.

DISCUSSION

Our findings suggest the potential for an association between lifetime exposure to estrogen and PSP. We did not find a relationship between estrogen exposure duration and PSP. Although the composite estrogen score did not reach statistical significance, the results suggest that increased overall exposure to estrogen might lower the risk of PSP. We also found that ERT use was associated with a lower risk of PSP. Among PSP cases, early age at menarche was associated with a decrease of 0.6 H&Y stage and 5.2 UPDRS II scores compared to those with normal or late age at menarche.

These findings are similar to results of some prior studies of other neurodegenerative diseases such as PD and AD. ERT use was associated with approximately 50% lower odds of PD^{23, 26} and with milder impairment in motor function in PD.^{27, 28} Increased lifetime exposure to estrogen has been found to be associated with decreased risk of developing PD,^{23, 26} and a delayed onset of PD.^{25, 28} Observational studies found that longer estrogen exposure was associated with a decrease of risk for cognitive impairment.^{22, 29} Genetic variants of aromatase, a rate-limiting enzyme for estradiol biosynthesis, has been found to be associated with an increased risk for AD.^{30, 31, 25} In contrast to these positive associations between estrogen and neurodegenerative diseases, a few studies found no association between estrogen and risk of PD,⁸ and risk of AD.³² Furthermore, meta-analysis of randomized controlled trials of ERT in dementia does not provide an evidence to prevent cognitive impairment.³³ Differences in the evaluation of estrogen exposure in clinical studies may contribute to the diverging findings regarding the role of estrogen in neurodegenerative diseases.

In vitro and animal studies consistently suggest a neuroprotective role of estrogen.¹ The possible mechanism of neuroprotection by estrogens includes anti-inflammatory activity, inhibition of oxidative stress and mitochondrial dysfunction, and increased expression of neurotrophic factors.³⁴ Additionally, estrogen may be involved in the reduction of hyperphosphorylated tau through activation of phosphatidyl inositol 3 kinase (PI3K)/AKT (protein kinase B), which inhibits glycogen synthase kinase 3 β (GSK3 β).³⁵ All these mechanism including oxidative injury, mitochondrial dysfunction, and chronic inflammation, is presumed to be associated with the pathomechanism of PSP.^{11, 36} Hyperphosphorylation of tau is the key pathomechanism of tauopathies and GSK3 β is an important tau protein kinase involved in the phosphorylation of tau.³⁷ Estrogen receptor modulators may also decrease hyperphosphorylation of tau.³⁸ Therefore, given the possible neuroprotective role of estrogens, increased exposure to estrogens may have an effect of neuroprotection in PSP through inhibition of tau pathology and inhibition of neurodegenerative conditions.

Strengths of this study include

(1) a relatively large sample size for a case-control study such a rare neurodegenerative disorder and comparable sample size with most case-control studies in PD;^{7, 24, 39} (2) high specificity of clinical diagnostic criteria for PSP, where all physicians were experienced movement disorder specialists from tertiary centers and were trained to use standardized disease severity measures; (3) inclusion of incident rather than prevalent PSP cases, thus reducing the likelihood of reverse causation; (4) use of a validated (Stewart) questionnaire; and (5) questionnaire administration over the telephone to all participants by trained raters at the central site. We also acknowledge that this study has limitations. Estrogen exposures may have been misclassified, as we estimated participants' age at menopause and specific ERT formulations were not available, and women may incorrectly recall their reproductive characteristics. We used a composite estrogen score using four variables including history of hysterectomy. We acknowledge that age at surgery might influence levels of estrogens, but this information was unavailable. Lastly, we cannot exclude that our findings might be found by chance, especially after examining multiple comparisons.

In conclusion, this study suggests a potentially protective role of lifetime estrogen exposure in PSP. Further research is needed to clarify the role of estrogen in PSP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Schematic representation for calculation of reproductive characteristics

Table 1

Reproductive characteristics of female PSP cases and controls and ORs (95% CI)

Reproductive Characteristics ^a	Cases (n=150)	Controls (n=150)	P value ^b	OR ^c (95% CI)	P value
Age at menarche, y	12.8 ± 1.5	12.4 ± 1.4	0.04	1.19 (1.00-1.42)	0.06
Early age at menarche	30 (20.0)	11 (7.33)	0.82	0.95 (0.37 - 2.48)	0.91
Age at menopause, y	50.6 ± 6.7	51.2 ± 6.1	0.58	0.99 (0.95 - 1.02)	0.41
Late age at menopause	63 (42.0)	71 (47.3)	0.35	0.68 (0.41 - 1.13)	0.13
Reproductive period, y	37.8 ± 6.7	38.7 ± 6.3	0.34	0.98 (0.95 - 1.02)	0.30
Estrogen length, y	47.1 ± 8.1	47.8 ± 8.2	0.77	1.02 (0.96 - 1.09)	0.51
Surgery history			0.59		0.47
No surgery [ref]	92 (62.2)	84 (58.3)		1.00	
Hysterectomy and/or unilateral oophorectomy	33 (22.3)	31 (21.5)		0.79 (0.40 - 1.56)	
Hysterectomy and bilateral oophorectomy	23 (15.5)	29 (20.1)		0.65 (0.34 - 1.25)	
Ever use oral contraceptives			0.97		0.74
Yes	98 (65.3)	97 (65.1)		1.11 (0.60 - 2.03)	
No [ref]	52 (34.7)	52 (34.9)		1.00	
Duration oral contraceptive use, y	8.1 ± 7.5	8.9 ± 8.1	0.47	0.99 (0.94 - 1.04)	0.65
Ever use ERT			0.009		0.03
Yes	55 (38.2)	78 (53.4)		0.52 (0.30 - 0.92)	
No [ref]	89 (61.8)	68 (46.6)		1.00	
Duration ERT use, y	10.6 ± 8.0	9.9 ± 7.3	0.61	0.98 (0.91 - 1.06)	0.51
Composite estrogen score			0.26		0.06 ^d
0 [ref]	44 (30.3)	31 (21.0)		1.00	
1	37 (25.5)	38 (25.7)		0.51 (0.24 - 1.09)	
2	38 (26.2)	44 (29.7)		0.46 (0.22 - 0.98)	
3 + 4	26 (17.9)	35 (23.7)		0.49 (0.19 - 1.01)	

PSP, progressive supranuclear palsy; OR, odds ratio; CI, confidence interval; ref, reference; ERT, estrogen replacement therapy; y, years

^aMeans ± standard deviations are reported for all continuous variables; frequencies and proportions are reported for all categorical variables.^bT-tests were performed to compare means; chi-squared tests were performed to compare proportions^cORs are adjusted for race/ethnicity, years of education, and smoking duration

The p-value refers to a p linear-trend.
 p

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