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BRIEF REPORTS

Lifetime Exposure to Estrogen and Progressive Supranuclear Palsy: Environmental and Genetic PSP Study

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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 ($P = .06$). Any exposure to estrogen replacement therapy halved the risk of PSP (odds ratio = 0.52; 95% confidence interval = 0.30-0.92; $P = .03$). Among PSP cases, earlier age at menarche was associated with better performance on Hoehn and Yahr stage ($\beta = -0.60$; SE = 0.26; $P = .02$) and Unified Parkinson's Disease Rating Scale II score ($\beta = -5.19$; SE = 2.48; $P = .04$) 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. © 2018 International Parkinson and Movement Disorder Society
Key Words: progressive supranuclear palsy; parkinsonism; estrogen; estrogen replacement therapy; case-control study

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 PD[5-8] and AD[9,10] do not provide consistent evidence for a protective role for estrogen. To our knowledge, the

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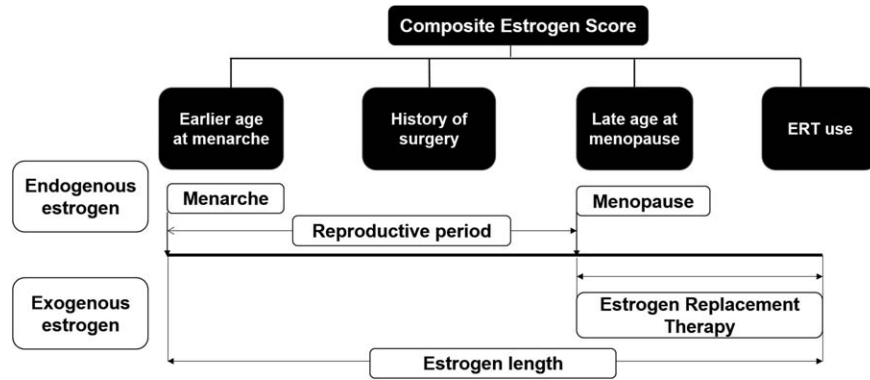

FIG. 1. Schematic representation for calculation of reproductive characteristics. ERT, estrogen replacement therapy.

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.

Methods
Study Population

The Environmental and Genetic–PSP study enrolled 350 incident PSP cases and 300 controls from 15 sites across North America.[11] PSP was defined using the National Institute of Neurological Disorders and Stroke-Society for PSP criteria.[12] Cases were requested to identify age-($\pm$ 5 years) and sex-matched, nonblood relatives as controls. Cases were excluded from this parent study if they scored < 24 on the MMSE[13] and controls were excluded if they scored < 28 on the Telephone Interview of Cognitive Status[14] or scored $\geq$ 4 on the Telephone Questionnaire for PD.[15] The 300 matched pairs were 50% men and 50% women. The analysis included 150 women with PSP and 150 age-matched control women (see Supplementary Fig.). This study was approved by the institutional review boards of all participating sites. All study participants provided written informed consent prior to participating in the study.

Study Procedures

The modified version of the Stewart telephone questionnaire[16] was administered to participants to collect demographic and reproductive characteristics. The participants were asked about exposures to endogenous estrogen; ages at menarche and last menstrual cycle; and exposure to exogenous estrogen, such as 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 whether they previously had a hysterectomy and/or oophorectomy.

To determine disease severity, the PSP Rating Scale,[17] Unified Parkinson Disease Rating Scale (UPDRS; I,

mentation; II, activities of daily living; III, motor examination),[18] modified Hoehn and Yahr stage,[19] MMSE,[13] Mattis Dementia Rating Scale-2,[20] California Verbal Learning Test Second Edition, and Frontal Assessment Battery[21] were administered to all PSP cases. Controls were administered the Telephone Interview of Cognitive Status[14] and Telephone Questionnaire for PD.[15] The questionnaires were administered 1 to 4 weeks after the cases' evaluations, depending on participant availability. The participants were recruited between October 1, 2006, and February 1, 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 4 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 1 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]

TABLE 1. Reproductive characteristics of female PSP cases and controls and ORs (95% CI)

Reproductive characteristic[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	.04	1.19 (1.00-1.42)	.06
Early age at menarche	30 (20.0)	11 (7.33)	.82	0.95 (0.37-2.48)	.91
Age at menopause, y	50.6 ± 6.7	51.2 ± 6.1	.58	0.99 (0.95-1.02)	.41
Late age at menopause	63 (42.0)	71 (47.3)	.35	0.68 (0.41-1.13)	.13
Reproductive period, y	37.8 ± 6.7	38.7 ± 6.3	.34	0.98 (0.95-1.02)	.30
Estrogen length, y	47.1 ± 8.1	47.8 ± 8.2	.77	1.02 (0.96-1.09)	.51
Surgery history			.59		.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			.97		.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	.47	0.99 (0.94-1.04)	.65
Ever use ERT			.009		.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	.61	0.98 (0.91-1.06)	.51
Composite estrogen score			.26		.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.
[a]Means ± standard deviations are reported for all continuous variables; frequencies and proportions are reported for all categorical variables.
[b]t-tests were performed to compare means; chi-squared tests were performed to compare proportions.
[c]ORs are adjusted for race/ethnicity, years of education, and smoking duration.
[d]The P value refers to a P linear trend.

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 the participants was 68.7 ± 6.5 years. Of the PSP cases, 93% and 98% of controls identified themselves as white (P = .05). Controls were more educated than cases (P = .003). PSP cases and controls reported 10.4 ± 19.0 and 6.6 ± 15.5 smoking pack-years, respectively (P = .04). Race/ethnicity, education, and smoking duration were adjusted for in all models. Of the women, 40% reported a previous hysterectomy and/or oophorectomy. ERT was reported by significantly more controls than cases (P = .009; Table 1). Although there was no association between estrogen exposure duration and PSP (OR = 1.02; 95% CI = 0.96-1.09; P = .51), there was a suggestion of inverse association between composite estrogen score and PSP that did not reach statistical significance (P = .06). When compared with 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 = .06). In addition, we found an association between using ERT and decreased risk of PSP (OR = 0.52; 95% CI = 0.30-0.92; P = .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 an improved California Verbal Learning Test–Second Edition cued recall score, the improvement per year increase was clinically minimal (β = 0.08; standard error (SE) = 0.04; P = .04). Early age at menarche was associated with less severe Hoehn and Yahr stage (β = −0.60; SE = 0.26; P = .02) and UPDRS II (β = −5.19; SE = 2.48; P = .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 Hoehn and Yahr stage and 5.2

UPDRS II scores when compared with those with normal or late age at menarche.

These findings are similar to the 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.[25,30,31] 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, a meta-analysis of randomized controlled trials of ERT in dementia does not provide 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] In addition, estrogen may be involved in the reduction of hyperphosphorylated tau through activation of phosphatidyl inositol 3 kinase/protein kinase B, which inhibits glycogen synthase kinase 3β.[35] All of these mechanisms, including oxidative injury, mitochondrial dysfunction, and chronic inflammation, are presumed to be associated with the pathomechanism of PSP.[11,36] Hyperphosphorylation of tau is the key pathomechanism of tauopathies, and glycogen synthase kinase 3β 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 the inhibition of tau pathology and the inhibition of neurodegenerative conditions.

The strengths of this study include the following: (1) a relatively large sample size for a case-control study of such a rare neurodegenerative disorder and a comparable sample size with most case-control studies in PD[7,24,39]; (2) a 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) the inclusion of incident rather than prevalent PSP cases, thus reducing the likelihood of reverse causation; (4) the 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 4 variables including history of hysterectomy. We acknowledge that age at surgery might influence levels of estrogens, but this information was unavailable. Finally, we acknowledge that we examined multiple estrogen exposures and our findings may be due to chance.

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. ■

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's website.

Selected Health and Lifestyle Factors, Cytosine-Adenine-Guanine Status, and Phenoconversion in Huntington's Disease

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