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Association Between High Serum Estradiol Levels and Delirium Among Hospitalized Elderly Women

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ABSTRACT

Background: Delirium is a common and serious disorder among hospitalized elderly individuals. We investigated the association between serum estradiol levels and incident delirium. **Methods:** Longitudinal study of 141 women ≥ 70 years old admitted to a tertiary care hospital in Mexico City. All participants underwent a comprehensive geriatric assessment. Blood samples for cortisol and estradiol determination were obtained at hospital admission. Incident delirium was investigated until participants were discharged. Multivariate models were run to test the independent association between estradiol levels and incident delirium. **Results:** Twenty-three (16.3%) participants developed delirium. Estradiol levels were higher among women with incident delirium compared with non-affected women. Multivariate logistic regression analysis showed that serum estradiol levels were associated with incident delirium even after adjusting for multiple confounding covariates, including cortisol levels (OR: 1.93; 95% CI: 1.28-2.92). **Conclusions:** Elderly women with high serum estradiol levels at hospital admission had an increased risk for incident delirium. Serum estradiol may be a biomarker for increased risk of delirium. (REV INVEST CLIN. 2015;67:20-4)
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INTRODUCTION

Delirium is a common and serious disorder among elderly individuals associated with adverse health-related outcomes[1]. This geriatric syndrome is the result of a complex interaction between predisposing and precipitating factors, some of which may be considered non-modifiable. Gender has been proposed to be one of these factors, although convincing evidence is lacking[2].

It has been proposed that differences in hormone levels between sexes may play a role in the development of delirium since estrogens are involved in multiple

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cognitive processes and their deficit has been associated with higher risks of dementia and neuropsychiatric symptoms[3,4]. Estrogens are involved in maintaining cognition through several pathways, including neurotrophic and neuroprotective effects in the brain. Gonadal hormones may also act as neurosteroids since they can be synthetized in the central nervous system, thereby rapidly altering cognitive functions. In postmenopausal women, gonadal hormone levels drop to practically undetectable levels. Estradiol (E2), which is capable of modulating cognition, is significantly low in elderly women, with serum levels ≤ 59 pg/ml expected in this population[5]. In addition, some authors propose that an age-related estrogen receptor alpha/estrogen receptor beta (ERa/ERb) expression combined with low E2 levels may contribute to different effects of estrogens on transcription, cell signaling, neuroprotection, and neuronal growth in the elderly[6]. However, the possible involvement of estrogens in the physiopathology of delirium has not been described. The purpose of this study was to investigate the association between serum E2 levels and incidence of delirium in a sample of hospitalized elderly women.

METHODS

Study population

This longitudinal study was conducted at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ), a tertiary care, university affiliated hospital in Mexico City. Participants were women aged 70 and older consecutively admitted between September 2009 and May 2010 from the emergency room to a medical ward; patients should not have had evidence of delirium and should have been hospitalized for at least 48 hours. Patients initially admitted to the intensive and intermediate care units were included only if they had no evidence of delirium before being transferred to a medical ward. Patients under treatment with steroids or estrogens were excluded. The sample size was calculated with the formula used to estimate a proportion based on the frequency of delirium previously described for this population (incident delirium rate of 12%)[7], with α = 5% and β = 20%. The hospital´s Ethics Committee approved the study protocol; all participants signed an informed consent.

Follow-up

Within the first 48 hours of admission, a comprehensive geriatric assessment was performed. The morning after admission, a blood sample was obtained to determine serum E2 and cortisol concentrations. All subjects were re-evaluated for delirium every day until discharged. Incident delirium and the procedures performed during hospitalization and other significant events were recorded.

Delirium diagnosis

Patients were evaluated using the Confusion Assessment Method (CAM)[8] within the first 48 hours of admission and then every 24 hours until discharged. Participants who met the CAM criteria were also evaluated for a definitive diagnosis of delirium following criteria of the Diagnostic and Statistical Manual of Mental Disorders (revised 4th ed.)[9].

Covariates

Sociodemographic variables included age, educational level, and marital status. Predisposing and precipitating factors for delirium were also investigated, including: visual and hearing impairment, pain, constipation, polypharmacy (use of ≥ 6 drugs), admission to ICU, history of alcohol abuse, history of stroke or delirium, opioid and benzodiazepine prescriptions, dementia, mild cognitive impairment, depression, and surgical and other invasive procedures (urinary catheterization, central venous catheterization, or mechanical ventilation).

Comorbidity was assessed using the Charlson Comorbidity Index (0-37 points; 0-1 = absence of comorbidity, 2 = mild, and ≥ 3 = severe)[10]. Body mass index (BMI = weight in kg/[height in m^2] ^{2}) was included as a covariate.

An adaptation of the Mini-Mental State Examination (MMSE)[11] was used to assess cognitive function on admission (0-30 points; a high score indicates better cognitive status).

Disability for activities of daily living (ADL; bathing, dressing, transferring from bed to chair, toileting, continence, and feeding) was assessed using Katz scale[12]. Activities of daily living disability was considered when

participants indicated that they were unable to perform at least one activity without help.

Laboratory procedures

In the morning after admission (7-8 am), 6 ml of peripheral blood was collected. Citrated plasma samples were extracted after one centrifugation and immediately stored at –40°C until tested. The E2 levels were measured by radioimmunoassay using COAT-A-COUNT kit (Siemens Medical Solutions Diagnostics; Los Angeles, CA, USA); intra-assay and inter-assay variation coefficients were 8.2 and 9.3%, respectively. The E2 concentrations were reported in pg/ml. Cortisol serum levels were determined by radioimmunoassay using a calibrated IMMULITE analyzer (Los Angeles, CA, USA); intra-assay and inter-assay variation coefficients were 7.7 and 8.5%, respectively. Cortisol levels were reported in ng/ml.

Statistical analysis

Variables are described using arithmetic means and standard deviations (SD) or frequencies and proportions where appropriate. Since E2 levels had an abnormal distribution, their logarithmic transformation was used for analyses. Chi square or Fisher's exact and Student´s t tests were used where appropriate. Univariate logistic regression models were created to describe the unadjusted effect of E2 levels (log-transformed) on delirium incidence. Interaction terms between E2 levels and predisposing factors for delirium as well as serum cortisol levels were run and entered into the model. A backward selection procedure at the 0.05 level was used to explore potential modifying effects between these variables and incident delirium. Multiple logistic regression analyses were done to test the independent association between E2 levels and incident delirium. All statistical analyses were performed at the 0.05 level and 95% confidence intervals (CI) were given. Statistical tests were performed using the SPSS software for Windows® (SPSS Inc., Chicago, IL, version 16.0).

RESULTS

During the study period 228 patients were screened for delirium and 86 were excluded (15 with delirium on admission, 32 with ≤ 48 hours of hospital stay, 21 were under steroid treatment, 15 had incomplete clinical information, and four declined to participate). The final sample was 141 subjects. Mean age was 77.8 years (SD: 5.6); most frequently self-reported chronic diseases were hypertension (65.2%) and diabetes (34%). Disability for ADL was found in 38.3%.

Twenty-three subjects (16.3%) developed incident delirium during hospitalization. Table 1 shows comparative analyses according to the incidence or not of delirium. Compared with the non-delirium group, those who developed delirium showed a trend towards being older ($p = 0.07$); they were more frequently visually impaired ($p < 0.01$); had higher rates of ADL disability ($p = 0.04$), higher frequency of previous stroke ($p < 0.01$), dementia ($p < 0.01$), and history of delirium ($p < 0.01$). In addition, participants with delirium had a higher incidence of ICU admission ($p = 0.01$), invasive procedures ($p < 0.01$), constipation ($p = 0.01$), and polypharmacy ($p = 0.04$).

Serum E2 and cortisol levels were higher in the incident delirium group compared with the non-delirium group; however, cortisol levels did not reach statistical significance. Likewise, cortisol levels were higher in women with high E2 (results not shown) ($p < 0.01$).

Univariate logistic regression analysis showed a significant association between E2 levels and incident delirium. After adjusting for multiple confounding variables (age, BMI, comorbidity, MMSE, previous history of delirium, BUN/Cr ratio, and cortisol levels), multivariate logistic regression analysis showed an independent association between E2 levels and incident delirium (OR: 1.93; 95% CI: 1.28-2.92; $p < 0.01$) (Table 2). No interaction terms entered in the model were statistically significant.

DISCUSSION

To our knowledge, this is the first report demonstrating an independent association between increased serum E2 levels and incident delirium in hospitalized elderly women.

Delirium has been associated with a wide range of biological markers, including cytokines, neurotransmitters, and hormones[13]. Stress conditions may potentiate the activation of the sympathetic nervous system, with the subsequent increase of cortisol and other stress

Table 1. Sociodemographic characteristics and health status associated with incident delirium in hospitalized elderly women

Variable	All subjects (n = 141)	Delirium (n = 23) (16.3%)	Delirium-free (n = 118) χ^2 (83.7%)	p
Variables:				
– Age, years, mean (SD)	77.8 (5.6)	79.4 (4.2)	77.5 (5.8)	0.07‡
– Educational level, mean (SD)	7.4 (4.9)	5.6 (4.5)	7.8 (5.0)	0.05‡
– Living at home, n (%)	140 (99.3)	23 (100)	117 (99.2)	0.65*
– Body mass index (kg/m^2), mean (SD)	25.3 (5.6)	25.6 (5.7)	25.3 (5.6)	0.77‡
– Visual impairment, n (%)	102 (72.3)	22 (95.7)	80 (67.8)	< 0.01*
– Hearing impairment, n (%)	30 (21.3)	4 (17.4)	26 (22.0)	0.61†
– Disability ≥ 1 ADL task, n (%)	54 (38.3)	13 (56.5)	41 (34.7)	0.04*
– Previous stroke, n (%)	17 (12.1)	8 (34.8)	9 (7.6)	< 0.01*
– Hypertension, n (%)	92 (65.2)	17 (73.9)	75 (63.6)	0.34*
– Diabetes mellitus, n (%)	48 (34.0)	10 (43.5)	38 (31.4)	0.29*
– Dementia, n (%)	6 (4.3)	4 (17.4)	2 (1.7)	< 0.01†
– Mild cognitive impairment, n (%)	15 (10.6)	3 (13)	12 (10.2)	0.71†
– Cancer, n (%)	37 (26.2)	6 (26.1)	31 (26.3)	0.98*
– History of delirium, n (%)	14 (9.9)	6 (26.1)	8 (6.8)	< 0.01*
– Alcohol abuse history, n (%)	5 (3.5)	1 (4.3)	4 (3.4)	0.99†
Events during hospitalization:				
– ICU admission, n (%)	4 (2.8)	3 (13.0)	1 (0.8)	0.01†
– Invasive procedures, n (%)	71 (50.4)	20 (87.0)	51 (43.2)	< 0.01*
– Constipation, n (%)	37 (26.2)	11 (47.8)	26 (22.0)	0.01*
– In-hospital polypharmacy, n (%)	113 (80.1)	22 (95.7)	91 (77.1)	0.04*
– Opioid use, n (%)	63 (44.7)	10 (43.5)	53 (44.9)	0.89*
– Benzodiazepine use, n (%)	48 (34.0)	7 (30.4)	41 (34.7)	0.69*
– Estradiol levels (pg/ml), GM	1.637	2.963	1.378	< 0.01‡
– Cortisol levels (ng/ml), mean (SD)	182.1 (86.9)	209.5 (97.1)	176.7 (84.2)	0.09*

*χ^2 test.
†Fisher's exact test.
‡Student's *t* test.
SD: standard deviation; ADL: activities of daily living; ICU: intensive care unit; GM: geometric mean.

hormones[14]. Elevated cerebrospinal fluid and serum cortisol levels have been found in several neuropsychiatric disorders including delirium[15]. However, in contrast with cortisol, increased serum E2 levels have not been described in patients with this entity. Nevertheless, serum E2 levels are elevated in other stressful situations[16,17].

Table 2. Multivariate logistic regression analysis of incident delirium among hospitalized elderly women

Variable	OR	95% CI	p
Unadjusted serum estradiol (log)	1.66	1.24-2.21	< 0.01
Adjusted serum estradiol (log)*	1.93	1.28-2.92	< 0.01

*Adjusted by age, body mass index, comorbidity (Charlson index), Mini-Mental State Examination, history of delirium, BUN/Cr ratio, and serum cortisol levels.
OR: odds ratio; CI: confidence interval.

A study carried out in the ICU setting showed that high serum E2 levels were associated with greater mortality. The authors hypothesized that such a finding could be related to an increase in peripheral aromatization of androgen to estradiol[17]. Another study demonstrated that androgen-to-estrogen aromatase activity was elevated in patients who underwent cardiac surgery[16]. Interestingly, androgen peripheral aromatization to E2 can also be induced by glucocorticosteroid exposure[18]. However, E2 alone is capable of raising serum cortisol concentrations. Regardless of this phenomenon's direction, E2 levels have been found to increase in stressful situations, usually in association with elevated serum corticosteroid levels.

In the present study serum cortisol levels were not significantly elevated in patients with or without incident

delirium, which suggests an alternative mechanism for the increase in E2. For instance, the proinflammatory cytokines that rise during infection may promote peripheral aromatase activity[19] and subsequently increase E2 concentrations.

Recent studies have also shown that high circulating levels of endogenous estrogens are significantly associated with myocardial no-reflow in postmenopausal women with acute myocardial infarction, even after adjusting for multiple cardiovascular risk factors. The underlying mechanism for such an association is still not well understood[20], yet it points to a possible vascular involvement, which may also be present in the case of delirium.

Other issues should be considered regarding this study's results. The main limitation may be that only a single determination of both hormones was carried out. In addition, total cortisol levels were not adjusted for serum albumin levels, a known factor influencing cortisol-binding globulin concentration. Finally, and due to the study's setting, selection bias may be present. However, the study describes an independent association between increased serum E2 levels and incident delirium even after adjusting for cortisol serum levels, which excludes the possibility of an epiphenomenon.

We hypothesize that the rise in E2 may be associated with an increased activity of peripheral aromatase, which in turn may be mediated by the presence of cortisol and proinflammatory cytokines. Given the clinical heterogeneity and multifactorial nature of delirium, it is possible that E2 contributes to its onset through several pathways. As stated before, the association of E2 with cortisol levels, inflammatory substances, and neurotransmitters makes E2 a possible target for further study in the search for a more complete description of delirium physiopathology. More studies are needed to determine whether E2 could be considered or not as a delirium biomarker.

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