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NOMBRE DEL ALUMNO

JUAN PABLO LEDESMA HEYER

NOMBRE DEL ASESOR

JOSE ALBERTO AVILA FUNES

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Association between Delirium and Higher Estradiol Serum Levels among Hospitalized Women

Juan Pablo Ledesma-Heyer,[1] Alfredo Reza-Albarrán,[2] Roberto Chavira-Hernández,[3] Lourdes Boeck-Quirasco,[3] and José Alberto Ávila-Funes[1,4]

[1] Department of Geriatrics. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México City, México

[2] Departament of Endocrinology and Metabolism. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México City, México

[3] Laboratory of Steroid Hormones. Departament of Reproductive Biology. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México City, México

[4] Centre de recherche Inserm, U897, Bordeaux, F-33076 France; Univ Victor Segalen Bordeaux 2, Bordeaux, F-33076 France

Corresponding Author:

José Alberto Ávila-Funes. Department of Geriatrics. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Vasco de Quiroga 15. CP 14000; Tlalpan, Distrito Federal, México. Phone: +52 (55) 54 87 09 00, 2258. E-mail: avilafunes@live.com.mx

Alternate Corresponding Author:

Juan Pablo Ledesma-Heyer. E-mail: doctor_geriatra@hotmail.com

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ABSTRACT

Background. Male gender is a known risk factor for *delirium* possibly related to hormone differences. Cholinergic deficiency and cortisol elevation are strong theories to explain its patophysiology. Estrogens participate in cognition and neuroprotection, but their role in *delirium* is not described yet. The purpose of this report is to investigate the association between serum levels of estradiol (E2) and incident *delirium*, as well as the possible role of cortisol in a sample of Mexican hospitalized elderly women.

Methods. In a longitudinal study we included 142 women aged 70 or older, without delirium on admission. We measured estradiol and cortisol levels and carried out an integral geriatric evaluation. We searched for delirium on a daily basis and had a registry of several potential confounders. Multiple logistic regression analyses were carried out to test the independent association between E2 serum levels and the incidence of *delirium*, adjusting for multiple covariates.

Results. 21 patients developed *delirium* (14.7%). Age range was 70 to 90 years. Delirious patients had more visual deficit (p = .006); higher disability for daily living activities (p = .049); and higher frequency of previous diagnosis of stroke/transient ischemic attack (p < .001), dementia (p = .001) or history of *delirium* (p = .009). Non-adjusted logistic regression analysis showed a significant association between E2 serum levels and incident *delirium* (Odds Ratio [OR] 1.67; 95% IC 1.25 to 2.24, p = .001). Logistic regression analysis showed that after the adjustment by multiple confounding variables there was an independent association between E2 serum levels and the incidence of *delirium* (OR 2.0; IC 95% 1.21 to 3.28, p = .007).

Conclusions. Those women with higher E2 serum levels at admission had increased incidence of *delirium*. E2 elevation in these patients could come from increased activity of peripheral aromatase enzyme mediated by cortisol or by proinflammatory cytokines. Elevated E2 may participate in the physiopathology of *delirium* interacting with the serotonergic, cholinergic or inflammatory system. More studies are needed in order to determine whether estradiol could be considered as a new biomarker for *delirium*.

Delirium is a neuropsychiatric disorder characterized by an acute and fluctuating change on the mental state where the inability of maintaining attention is predominant (1). Its presence in the elderly has been associated with an increase in the risk of length of hospital stays and costs as well as an increased risk of institutionalization and mortality (1-3). At admission, its prevalence and incidence are elevated (increased), more frequently at Intensive Care and Emergency Room (3, 4). Several theories have tried to explain the physiopathology of *delirium* as the imbalance of different neurotransmitters (cytokines, γ-aminobutyric acid, glutamate or serotonin activation, etc.) (5), though the cholinergic deficiency theory is the one with larger evidence (6), since administration of anticholinergic drug drugs can induce *delirium* in humans and animals, and serum anticholinergic activity is increased in patients with *delirium*. In addition, acetylcholine participates in attention and conscience level maintenance processes (7). However, stress response and cortisol excess involvement are also important in severely ill patients with this disorder (8,9).

In the elderly, *delirium* development depends on a complex interaction of predisposing and precipitating factors, some of which may be susceptible to interventions (1, 10). Sex is a well known predisposing factor for *delirium* with men being the most affected (1). Although there is no clear explanation, hormonal differences due to sex may be a part of it. It is known that estrogens participate in multiple cognitive processes (11), their presence confers a level of neuroprotection (12) and their deficit has been linked to higher risk of Alzheimer's disease (11) as well as increased severity of neuropsychiatric symptoms in older adults (13). Cerebral regions involved in attention, memory and alert state processes are influenced by acetylcholine as well as estrogens (14-16). In postmenopausal women, estrogens come mostly from the peripheral aromatization of androstenedione to estrone (which later becomes estradiol) (17, 18). Despite of their known role in cognitive function and being biologically plausible, in our knowledge, the

possible involvement of estrogens in the physiopathology of *delirium* in the elderly has not been described. Therefore, the purpose of this report is to investigate the association between serum levels of estradiol (E2) and incident *delirium*, as well as the possible role of cortisol in a sample of Mexican hospitalized elderly women.

METHODS

Study population

This is a longitudinal study of 142 consecutive hospitalized elderly women followed at a third level teaching hospital with approximately 130,000 visits per year and an affiliated Geriatrics residency program in Mexico City. All women aged 70 and older, without diagnosis of *delirium* at admission, and hospitalized for more than 48 hours were eligible for enrollment and were recruited consecutively by a clinically trained Geriatrician (JPLH). Patients with diagnosis of *delirium* or under steroid treatment or hormone replacement therapy with estrogens were excluded. The required sample size was estimated assuming an incident rate of *delirium* in our own hospital of 12% (4) with α=5% and ß=20%. The stated sample size provides sufficient power to detect significant differences for the incidence of *delirium*. The Local Ethical Committee approved the study, and all participants signed an informed consent.

Delirium diagnosis

Delirium (dependent variable) was identified through Confusion Assessment Method (CAM) (20) and defined according to the Diagnostic and Statistical Manual of Mental Disorders (4^{th} ed.) criteria revised elsewhere. “All patients were screened at admission and on a daily basis. When delirium developed no further screening was made”.

Blood Collection and measurements

Six cl of blood were obtained in the first 48 hours upon admission. Citrated plasma sample were obtained after one centrifugation. All samples were taken between 7:00 to 8:00 a.m. and immediately stored at -40°C before their analysis. E2 serum levels were measured by radioimmunoassay from Siemens Medical Solutions Diagnostics (Los Angeles, CA, USA) COAT-A-COUNT kit. The intra-assay and inter-assay variation coefficients were 8.2% and 9.3%, respectively. Values of E2 were reported in pg/ml. The concentration of serum cortisol was measured by radioimmunoassay using a calibrated IMMULITE analyzer (Los Angeles, CA, USA). The intra-assay and inter-assay variation coefficients were 7.7% and 8.5%, respectively. Cortisol serum levels were reported in ng/ml. Given that E2 serum levels had an abnormal score distribution, four levels were defined according to the quartiles of score distribution. The lowest quartile of the distribution indicates the lowest E2 serum levels.

Covariates

Socio-demographic variables included were age, educational level (years), and marital status. Variables known to be associated with *delirium* included here were: admission to intensive care during hospitalization; antecedent of alcoholism; visual and hearing deficit; antecedent of *delirium*; previous stroke; and known dementia, mild cognitive impairment or depression diagnosis (1-4).

Comorbidity was represented by the Charlson index, which includes 19 diseases (21). The presence of each of these diseases was summed up in a score ranging from 0 to 37 points, where is considered an absence of comorbidity 0 to 1 points, low comorbidity 2 points, and high $\geq$ 3 points.

The Mini-Mental State Examination (MMSE) (22) was used to assess global cognitive function (0 to 30 points; higher score indicates better cognitive status).

The number of drugs used was added and shown as a continuous variable. Polypharmacy (23) (≥ 6 drugs) as well as the use of opioids or benzodiazepines during hospitalization were treated as binomial categorical variables (yes or not).

Two measurements of disability were investigated: instrumental (IADL) and basic activities of daily living (ADL). For the IADL, participants reported their ability to perform 8 activities of daily living based on the Lawton & Brody scale: using the telephone, having responsibility for one's own medication, managing money, being able to transport oneself, shopping, cooking, doing housework, and doing laundry (the last three were only asked to women). For the ADL, participants were asked if they needed help for any task from the Katz ADL scale (bathing, dressing, transferring from bed to chair, continence, toileting, and feeding). For each domain of disability, if participants indicated that they were unable to perform one or more activities without help, they were considered as having IADL or ADL disability.

Body mass index (BMI, calculated from anthropometrical measurements) was used as a categorical variable as follows: low weight (< 18.5 kg/ m^2), normal weight (18.5-24.9 kg/ m^2), overweight (25-30.0 kg/m^2), and obesity (> 30 kg/m^2).

Surgeries, difficulty in controlling pain and constipation during hospitalization were treated as binomial categorical variables. The application of invasive procedures during the hospital stay included any of the following: urinary catheterization, central venous catheterization, and use of mechanical ventilation (invasive or non-invasive).

Procedure

Within the first 48 hours of hospitalization, an integral geriatric evaluation was performed which included about 120 items, lasting 20-45 minutes and which includes a wide range of information. It contains self-reported information regarding socio-demografic antecedents, drug use, health issues, functional state, nutritional assessment, mood and cognitive status, among others. Biological samples were obtained and processed as described above. Patients were followed on a daily basis until their discharge; recording incident *delirium* as well as procedures performed (surgery, and other invasive procedures), drugs used, admission to intensive care (ICU) and associated events (*delirium*, pain, constipation, etc.). All the information was entered in a database for later analysis.

Statistical analysis

Variables were described using arithmetic means and standard deviations (SD) or frequencies and proportions where appropriate. The distribution of the E2 serum levels was not normal therefore we used their log-transformations for analyses. Cortisol serum levels showed normal distribution. The statistical procedures of chi square and Student t tests were used as appropriate.

Univariate logistic regression models were used to describe the unadjusted effect of E2 serum levels (log-transformed) on incidence of *delirium*. Interaction terms between E2 and visual deficit, antecedent of dementia diagnosis, ICU admission, opioid and benzodiazepines use, previous delirium or alcoholism, BMI and cortisol serum levels were added to our model, and the backward selection procedure at the .05 level was used to explore the potential modifying effects between these variables and incident *delirium*. Multiple logistic regression analyses were carried out to test the independent association between E2 serum levels and the incidence of *delirium*,

adjusting for multiple covariates. All statistical tests were performed at the .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

In a period of 4 months, 228 women aged 70 and older were identified when admitted consecutively for hospitalization, from which 86 were excluded because of different reasons (15 with *delirium* at admission, 32 with short hospitalization < 48 h, 21 under steroid treatment, 14 incomplete clinical information, and 4 declined to participate). From the 142 patients of the final sample, 21 (14.7%) developed *delirium* during their hospital stay. Mean age was 77.8 (range 70 to 90 years). Hypertension (64.5%) was the most frequent chronic disease. The 66.2% of participants had disability for IADL, and 38% for ADL. Table 1 presents the socio-demographic and health characteristics of participants according to the development of *delirium* or not during hospitalization. In comparison to participants that did not develop *delirium*, those who developed it were older ($p = .068$); had more visual deficit ($p = .006$); higher disability for ADL ($p = .049$); and higher frequency of previous diagnosis of stroke/transient ischemic attack ($p < .001$), dementia ($p = .001$) or history of *delirium* ($p = .009$). During hospitalization, compared to those who did not develop *delirium*, those who did had a higher incidence of ICU admission ($p = .014$), invasive procedures application ($p < .001$), constipation ($p = .014$), and polypharmacy ($p = .049$). There were no differences related to *delirium* with the use of opioids or benzodiazepines, hearing deficit, disability for IADL, diabetes, mild cognitive impairment, history of cancer or alcoholism. E2 serum levels were found to be elevated in the group with incident *delirium* ($p < .001$) as well as, cortisol serum levels. Cortisol levels were found to be elevated on those women with high E2 levels ($p = .002$).

Non-adjusted logistic regression analysis showed a significant association between E2 serum levels and incident *delirium* (Odds Ratio [OR] 1.67; 95% IC 1.25 to 2.24, p = .001). Logistic regression analysis (Table 2) showed that after the adjustment by multiple confounding variables (age, BMI, comorbidity, MMSE, antecedent of *delirium*, visual deficit, invasive procedures, BUN/Cr ratio, admission to ICU, surgery, polypharmacy during hospital stay, ADL functionality and cortisol levels) there was an independent association between E2 serum levels and the incidence of *delirium* (OR 2.0; IC 95% 1.21 to 3.28, p = .007). No interaction term introduced in the models was statistically significant.

DISCUSSION

This study is the first, in our knowledge, that shows an association between elevated E2 serum levels at hospital admission and incident *delirium* in hospitalized elderly women, even after adjusting for potentially confounding variables. Serum cortisol levels were also elevated in patients who developed *delirium* though not in statistically significant manner.

Unlike cortisol, it is not clear what causes elevated estradiol in persons with *delirium*. Elevated cortisol levels in cerebrospinal fluid or serum have been shown in different neuropsychiatric alterations including *delirium* (8, 24, 25). In dementia patients there is also an alteration in the regulation of the hypothalamus-hypophysis axis, which lowers the threshold for *delirium* favoring the patients' *delirium* response in stressful situations (26). On the other hand, as well as cortisol (8, 26, 27), in stressful situations such as surgery, acute disease or pain, an elevation of E2 is present (28, 29). In such situations, there is a drop in testosterone, luteinizing hormone, and follicle-stimulating hormone due to a negative regulation of the hypothalamic liberation of gonadotropin-releasing hormone and also a drop in the expression of its pituitary receptors ("hypogonadotrophic hypogonadism due to acute disease") (30-32). However, an E2

elevation could not be solely explained by a generalized hyperactivity of the hypothalamus-hypophysis axis. In a study performed on patients aged 55.1 in average (hospitalized in surgical and trauma intensive care unit), it was observed higher mortality in those who had elevated serum estradiol- including men-, which was explained by the increase of peripheral aromatization of androgens to estradiol, thought no mention if development of *delirium* was investigated (29).

Another study which included male and female patients (between 42-69 years) who underwent cardiac surgery showed that androgen to estrogen aromatase enzyme activity is increased in stressful situations, increasing estrone and estradiol levels (28). One more study showed a significant formation of estrogens in adipose tissue cells induced by the infusion of glucocorticosteroids. Specifically with dexamethasone and cortisol in high doses, the rate of aromatization is considerably increased (33). It could be thus explained why in stressful situations (eg, hospitalization) cortisol elevation, as a consequence, directly induces the peripheral aromatase activity and therefore elevated estradiol levels. There is also the possibility that estradiol increases cortisol levels directly. It was demonstrated in animal models that estradiol infusion induced hypersensitivity to adrenocorticotropic hormone and so it boosted the adrenocortical response (34). However, as showed in this study, E2 were associated with incident *delirium* independently of cortisol levels, which suggests an alternative mechanism, not mediated by, in its physiopathology.

Another means of interaction between *delirium* and estrogens is through the regulation of stress response mediated by the immune system. It has been demonstrated that systemic infections and proinflammatory cytokines (interleukin-1, interleukin-6, tumor necrosis factor-alpha) are direct common triggers of *delirium* (35), but furthermore, the elevation of proinflammatory cytokines may directly induce peripheral aromatase activity (36) thereby elevating the concentration of estradiol.

Nonetheless, still does not know the exact mechanism of why elevated E2 levels may promote *delirium*. In animal models, estrogens modulate several neurotransmitters involved in the regulation of cognition, affection and sleep-awake cycle including acetylcholine, serotonin, cortisol, dopamine, and norepinephrine (37). A biologically plausible hypothesis is that *delirium* in patients with elevated E2 may be mediated by serotonin since serotonergic neurons are localized in brain areas that participate in cognition and mood (hippocampus, limbic system and the frontal cortex). It is worth mentioning that type 2A 5-hydroxytryptamine (5-HT) receptor is also found in several other systems and its participation in the regulation of anxiety, appetite, cognition, imagination, learning, memory, mood, perception, sexual behavior and sleep, among others has been demonstrated (37). Estrogens increased messenger RNA activity of 5-HT_{2A} receptor in the dorsal raphe nucleus. Estrogens also increase affinity to 5-HT_{2A} receptor in the frontal cortex, anterior cingulate gyrus, primary olfactory cortex, striate nucleus and nucleus accumbens (37). In a study of postmenopausal women, estrogen administration increased significantly the union of serotonin to 5-HT_{2A} receptors, especially in the prefrontal cortex, inferior frontal gyrus, medial frontal gyrus and anterior cingulated cortex (38), improving furthermore the performance in neuropsychological tests but without showing changes in mood (especially depressive mood) (38). Law regulates several 5-HT_{2A} receptor agonists since they often produce episodes of psychosis, hallucinations and depersonalization (eg. mescaline, psilocybin, LSD, etc.) (39). Curiously, several drugs used for the treatment of *delirium* are antagonists of 5-HT_{2A} receptors (quetiapine, olanzapine or risperidone) (40) (see Figure 1).

The main limitation of this study was that we were not able to know the behavior of E2 and cortisol levels throughout the length of the hospital stay, which could support the hypothesis of a relationship between higher E2 serum levels and the development of *delirium*. On the other hand, we did not adjust the total cortisol levels to those of albumin (since cortisol levels, by not

being free cortisol, can be influenced by the concentration of the cortisol-binding globulin). In addition, selection bias could exist because patients mainly come to our hospital for diagnosis or treatment of a medical disease; therefore, it had a low frequency of orthopedic or cardiothoracic surgery, both situations related to higher incidence of *delirium*.

However, in spite of the limits mentioned, the strength of the study includes analysis of the association between estrogens and the incidence of *delirium*, breaking ground for new hypotheses about its physiopathology. Given the clinical heterogeneity and multifactorial nature of *delirium*, it is likely that multiple pathogenic mechanisms include E2 as a contributor in the development of *delirium*. A similar longitudinal study should include the determination of several hormones, systemic inflammation markers (eg. proinflammatory cytokines) as well as measure the activity of aromatase in central adipose tissue.

This study shows that, during hospitalization of elderly women, those with higher E2 serum levels at admission are associated with increased incidence of delirium compared to those that had a low E2 levels. Cortisol participation in this association is independent and therefore hyperestrogenemia does not seem to correspond with an epiphenomenon due to hypercortisolemia. E2 elevation in these patients could come from increased activity of peripheral aromatase enzyme mediated by cortisol or by proinflammatory cytokines. Elevated E2 may participate in the physiopathology of *delirium* interacting with the serotonergic, cholinergic or inflammatory system. It is possible that the neuroprotection role of estrogens is decreased when they drop but also when they are excessively elevated, which could be described as a U-shaped curve effect of the estrogens on neurocognitive outcomes. However, studies are needed in order to determine whether estradiol could be considered as a new biomarker for *delirium*.

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REFERENCES

1. Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. *Nat Rev Neurol*. 2009;5:210-220.
2. Maldonado JR. Delirium in the acute care setting: characteristics, diagnosis and treatment. *Crit Care Clin*. 2008;24:657-722.
3. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age Ageing*. 2006;35:350-364.
4. Villalpando-Berumen JM, Pineda-Colorado AM, Palacios P, Reyes-Guerrero J, Villa AR, Gutierrez-Robledo LM. Incidence of delirium, risk factors, and long-term survival of elderly patients hospitalized in a medical specialty teaching hospital in Mexico City. *Int Psychogeriatr*. 2003;15:325-336.
5. Maldonado JR. Pathoetiological model of delirium: a comprehensive understanding of the neurobiology of delirium and an evidence-based approach to prevention and treatment. *Crit Care Clin* 2008;24:789-856.
6. Hshieh TT, Fong TG, Marcantonio ER, Inouye SK. Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence. *J Gerontol A Biol Sci Med Sci*. 2008;63:764-772.
7. Singh M, Setalo G Jr, Guan X, Warren M, Toran-Allerand CD. Estrogen-induced activation of mitogen-activated protein kinase in cerebral cortical explants: convergence of estrogen and neurotrophin signaling pathways. *J Neurosci*. 1999;19:1179-1188.
8. Shi CM, Wang DX, Chen KS, Gu XE. Incidence and risk factors of delirium in critically ill patients after non-cardiac surgery. *Chin Med J (Engl)*. 2010;123:993-999.
9. Lupien SJ, Maheu F, Tu M, Fiocco A, Schramek TE. The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition. *Brain Cogn*. 2007;65:209-237.

10. Inouye SK, Bogardus ST Jr, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med*. 1999;340:669-676.
11. Sherwin BB. Estrogen and cognitive functioning in women. *Endocr Rev*. 2003;24:133-151.
12. Behl C. Oestrogen as a neuroprotective hormone. *Nat Rev Neurosci.* 2002;3:433-442.
13. Senanarong V, Vannasaeng S, Poungvarin N, et al. Endogenous estradiol in elderly individuals: cognitive and noncognitive associations. *Arch Neurol.* 2002;59:385-389.
14. Sherwin BB. Estrogen effects on cognition in menopausal women. *Neurology* 1997;48(Suppl 7):S21-S26.
15. Singh M, Meyer EM, Simpkins JW. The effect of ovariectomy and estradiol replacement on brain-derived neurotrophic factor messenger ribonucleic acid expression in cortical and hippocampal brain regions of female Sprague-Dawley rats. *Endocrinology*. 1995;136:2320-2324.
16. Davies P, Maloney AJ. Selective loss of central cholinergic neurons in Alzheimer's disease. *Lancet*. 1976;2:1403.
17. Badeau M, Vihma V, Mikkola TS, Tiitinen A, Tikkanen MJ. Estradiol fatty acid esters in adipose tissue and serum of pregnant and pre- and postmenopausal women. J Clin Endocrinol Metab 2007; 92(11):4327-31.
18. Gruber CJ, Tschugguel W, Schneeberger C, Huber JC. Production and actions of estrogens. N Engl J Med 2002; 346(5):340-52.
19. Simpson E, Rubin G, Clyne C, et al. Local estrogen biosynthesis in males and females. *Endocr Relat Cancer.* 1999;6:131-137.
20. Inouye SK, van Dyck CH, Alessi CA, et al.. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med*. 1990;113:941-948.
21. Charlson ME, Charlson RE, Peterson JC, et al. The Charlson comorbidity index is adapted

to predict costs of chronic disease in primary care patients. *J Clin Epidemiol.* 2008;61:1234-1240.

22. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
23. Bushardt RL, Massey EB, Simpson TW, Ariail JC, Simpson KN. Polypharmacy: misleading, but manageable. *Clin Interv Aging.* 2008;3:383-389.
24. Maclullich AM, Ferguson KJ, Miller T, de Rooij SE, Cunningham C. Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. *J Psychosom Res.* 2008;65:229-238.
25. Pearson A, de Vries A, Middleton SD, et al. Cerebrospinal fluid cortisol levels are higher in patients with delirium versus controls. *BMC Res Notes*. 2010;3:33.
26. Robertsson B, Blennow K, Brane G, et al. Hyperactivity in the hypothalamic-pituitary-adrenal axis in demented patients with delirium. *Int Clin Psychopharmacol.* 2001;16:39-47.
27. Olsson T, Marklund N, Gustafson Y, Nasman B. Abnormalities at different levels of the hypothalamic-pituitary-adrenocortical axis early after stroke. *Stroke*. 1992;23:1573-1576.
28. Spratt DI, Morton JR, Kramer RS, Mayo SW, Longcope C, Vary CP. Increases in serum estrogen levels during major illness are caused by increased peripheral aromatization. *Am J Physiol Endocrinol Metab.* 2006;291:E631-E638.
29. May AK, Dossett LA, Norris PR, et al. Estradiol is associated with mortality in critically ill trauma and surgical patients. *Crit Care Med.* 2008;36:62-68.
30. Christeff N, Benassayag C, Carli-Vielle C, Carli A, Nunez EA. Elevated oestrogen and reduced testosterone levels in the serum of male septic shock patients. *J Steroid Biochem.* 1988;29:435-440.
31. Adams TE, Sakurai H, Adams BM. Effect of stress-like concentrations of cortisol on

estradiol-dependent expression of gonadotropin-releasing hormone receptor in orchidectomized sheep. *Biol Reprod.* 1999;60:164-168.

32. Spratt DI, Cox P, Orav J, Moloney J, Bigos T. Reproductive axis suppression in acute illness is related to disease severity. *J Clin Endocrinol Metab.* 1993;76:1548-1554.
33. Simpson ER, Ackerman GE, Smith ME, Mendelson CR. Estrogen formation in stromal cells of adipose tissue of women: induction by glucocorticosteroids. *Proc Natl Acad Sci U S A.*1981;78:5690-5694.
34. Figueiredo HF, Ulrich-Lai YM, Choi DC, Herman JP. Estrogen potentiates adrenocortical responses to stress in female rats. *Am J Physiol Endocrinol Metab.* 2007;292:E1173-E1182.
35. van Gool WA, van de Beek D, Eikelenboom P. Systemic infection and delirium: when cytokines and acetylcholine collide. *Lancet*. 2010;375:773-775.
36. Simpson ER, Davis SR. Minireview: aromatase and the regulation of estrogen biosynthesis--some new perspectives. *Endocrinology.* 2001;142:4589-4594.
37. Amin Z, Canli T, Epperson CN. Effect of estrogen-serotonin interactions on mood and cognition. Behav Cogn Neurosci Rev. 2005;4:43-58.
38. Kugaya A, Epperson CN, Zoghbi S, et al. Increase in prefrontal cortex serotonin 2A receptors following estrogen treatment in postmenopausal women. *Am J Psychiatry.* 2003;160:1522-1524.
39. Gonzalez-Maeso J, Weisstaub NV, Zhou M, et al. Hallucinogens recruit specific cortical 5-HT(2A) receptor-mediated signaling pathways to affect behavior. *Neuron.* 2007;53:439-452.
40. de Angelis L. 5-HT2A antagonists in psychiatric disorders. *Curr Opin Investig Drugs.* 2002;3:106-12.

Table 1 Sociodemographic characteristics and health status of participants with or without *delirium*

Variable	All *n* = 142	*Delirium* Present *n* = 21 (14.7%)	*Delirium* Absent *n* = 121 (85.2%)	*P*
Age, years, mean (SD)	77.8 (5.6)	79.4 (4.2)	77.5 (5.8)	.068
Education, years, mean (SD)	7.4 (4.9)	5.6 (4.5)	7.8 (5.0)	.052
Living at home (%)	n99.3	100	99.2	.658
Body mass index (kg/m^2), mean (SD)	25.7 (5.4)	25.6 (5.6)	25.7 (5.4)	.976
Visual impairment (%)	n72.5	95.7	67.8	.006
Auditory deficit (%)	n21.1	17.4	22	.619
Disability ≥ 1 ADL task (%)	n38	56.5	34.7	.049
Disability ≥ 1 IADL task (%)	n66.2	73.9	65.3	.420
Stroke / TIA (%)	n12	34.8	7.6	< .001
Hypertension (%)	n64.5	73.9	62.7	.304
Diabetes (%)	n33.8	43.5	31.4	.259
Dementia (%)	n4.2	17.4	1.7	.001
Mild Cognitive Impairment (%)	n10.6	13	10.2	.683
Cancer (%)	n26.8	26.1	26.3	.985
Antecedent of *delirium* (%)	n10.6	26.1	7.6	.009
History of alcoholism (%)	n3.5	4.3	3.4	.595
Events during hospitalization:				
ICU admission (%)	n2.8	13	0.8	.014
Invasive procedures (%)	n50	87	43.2	< .001

Constipation (%)	n26.8	47.8	22.9	.014
In-hospital polypharmacy (%)	n80.3	95.7	78	.049
Opioid use (%)	n44.4	43.5	44.9	.899
Benzodiacepine use (%)	n34.5	30.4	35.6	.635
Log Estradiol, GM	1.637	2.963	1.585	<.001
Cortisol levels (ng/ml), mean (SD)	1.64 (1.9)181±88	209.5 (97.1)	175.8 (85.4)	.092

ADL = Basic activities of daily living (self-reported disability)

IADL = Instrumental activities of daily living (self-reported disability).

TIA = Transient ischemic attack.

ICU = Intensive care unit

GM = Geometric mean

Table 2. Multivariate logistic regression analysis of incident *delirium*.

VARIABLE	OR	95% CI	*p*
Unadjusted serum estradiol (*log*)	**1.67**	**1.25 to 2.24**	**.001**
Adjusted serum estradiol (*log*)*****	**2.0**	**1.21 to 3.28**	**.007**

[*]*Note:* Adjusted for age, body mass index, comorbidity (Charlson index), mini-mental State Examination, antecedent of *delirium*, visual impairment, invasive procedures (urinary catheter, central catheter or mechanical ventilation), BUN/Cr ratio, ICU admission, polypharmacy in hospital, basic activities of daily living disability, and serum cortisol levels.

OR = Odds ratio

CI = Confidence intervals.

Figure legends

Figure 1. Outlining the relationship between a stressful event (lightning) and cortisol, estradiol, interleukins (IL) and *delirium* through peripheral aromatase activity. We introduce the theoretical potential involvement of the serotonergic system, specifically through 2A 5-hydroxytryptamine receptor. TNFa: tumor necrosis factor - alpha.

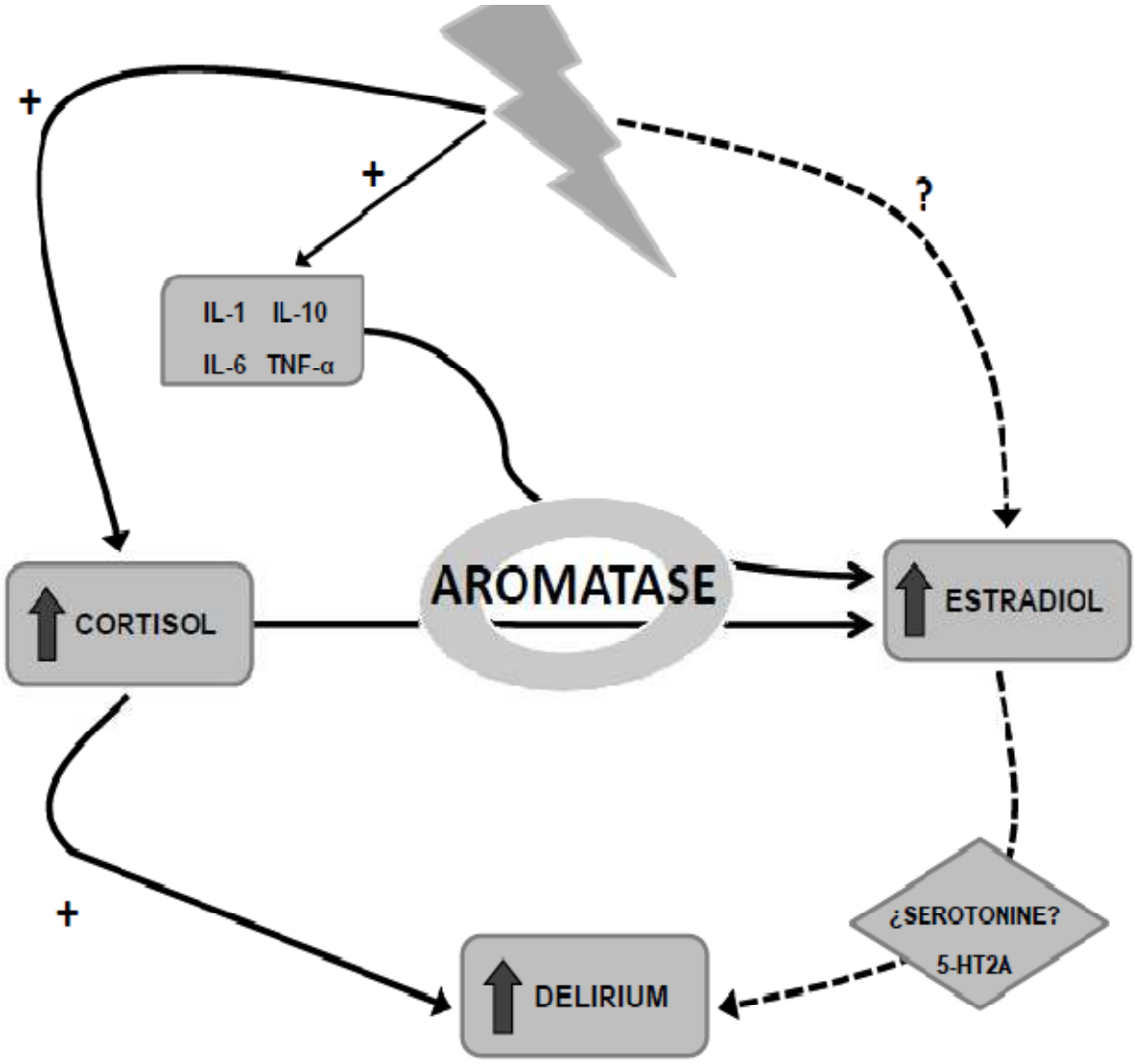
Table 1.

Overall clinical and demographic description

Total (*n*)	142
Delirium (%)	14.7
Age, years (SD)	77.8±5.6
Education, years (SD)	7.6±4.2
Living at home (%)	99.3
Emergency room admission (%)	20.4
General floor admission (%)	61.3
Geriatric floor admission (%)	18.3
UTI admission during hospitalization (%)	2.8
Surgery (%)	37.3
BMI (kg/m^2, SD)	25.7±5.4
MMSE (SD)	25.4±5.0
Disability – Katz ADL (%)	38
Disability – IADL (%)	66
Comorbility – Charlson score (SD)	2.2±1.6
Stroke / TIA (%)	12
Diabetes (%)	33.8
Dementia (%)	4.2
Mild Cognitive Impairment (%)	10.6
Antecedent of *delirium* (%)	10.6
History of alcoholism (%)	3.5

Visual impairment (%)	72.5
Auditory deficit (%)	21.1
Drugs used during hospitalization (#, SD)	5±3
Polypharmacy during hospitalization (%)	80.3
Cortisol levels (ng/ml, SD)	181±88
Estradiol levels (pg/ml, SD)	28.1±8.9

Figure 1.


+
+
?
IL-1 IL-10
IL-6 TNF-α
CORTISOL
AROMATASE
ESTRADIOL
+
¿SEROTONINE?
5-HT2A
DELIRIUM