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Associations between sex hormones and cognitive and neuropsychiatric manifestations in vascular dementia (VaD)

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ABSTRACT

Although numerous studies have been carried out to determine the effects of sex hormones on Alzheimer's disease (AD), little is known about the associations between sex hormones and VaD. The aim of this study was to compare serum sex hormone levels between VaD patients and normal controls, and to further determine the link between sex hormones and cognitive and neuropsychiatric manifestations of VaD. Serum levels of total estradiol (TE2), total testosterone (TT), luteinizing hormone (LH), and sex hormone binding globulin (SHBG) were measured in 87 VaD patients and 110 cognitive normal controls. The levels of bioavailable estradiol (BE2) and bioavailable testosterone (BT) were calculated. The VaD patients underwent the tests of global cognitive function, verbal memory, and visuospatial, and executive ability. The Neuropsychiatric Inventory (NPI) was used to assess neuropsychiatric symptoms. Compared to controls, the testosterone and SHBG levels were lower in male VaD patients, and the estradiol levels were higher in female VaD patients. The hormones levels were not correlated with cognitive functions among either male or female VaD patients. There were no associations between hormone levels and neuropsychiatric symptoms among male patients, while the TE2 and TT levels were positively associated with apathy and anxiety, respectively among female patients. Our findings suggested there were sex hormone level changes in VaD patients in comparison with cognitive normal controls. Sex hormones were associated with neuropsychiatric symptoms among female but not male VaD patients.

1. Introduction

The higher prevalence and risk of dementia in women found in previous studies (Bachman et al., 1992; Fratiglioni et al., 1997) drew the attention of researchers to the effects of estrogen, which declines rapidly after menopause. Numerous laboratory studies have suggested the neuroprotective roles of estrogen against cognitive decline. However, in real population, the effects of estrogen on dementia are still ambiguous. Compared to the considerable studies on the associations between sex hormones and AD, the effects of sex hormones on VaD were much less explored, though the influences of sex hormones on vascular function and stroke have been extensively discussed. A few previous studies investigated the association between sex hormone levels and the risk of VaD, and the results were inconsistent. Some suggested higher levels of estrogen increased the risk of VaD in women (Geerlings et al., 2003); however, other studies observed no association between estrogen levels and the risk of VaD in females (Ravaglia et al., 2007). For men, no previous studies found the association between estrogen or testosterone levels and the risk of VaD (Geerlings et al., 2003, 2006; Ravaglia et al., 2007).

The serum sex hormone levels are not only associated with the risk of dementia, but also with the clinical presentations of dementia. Sex hormones are related to different cognitive domain impairments and neuropsychiatric symptoms of AD. Testosterone supplementation may benefit selective cognitive functions in men with AD (Cherrier et al., 2005). Significant effects of estrogen treatment were observed on attention, verbal memory, and visual memory among female AD patients (Asthana et al., 2001). With respect to neuropsychiatric symptoms, plasma testosterone levels were positively and estrogen levels were negatively correlated with aggression in men with dementia (Orengo, Kunik, Molinari, Wristers, & Yudofsky, 2002), and estrogen treatment was reported to ameliorate depression in women with AD (Valen-Sendstad et al., 2010). These studies suggest that there may be gender specific effects of sex hormones on cognitive and neuropsychiatric manifestations of dementia. However, to our knowledge, there

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was no previous study investigating the associations between sex hormones and cognitive functions or neuropsychiatric symptoms of VaD, though gender differences in clinical presentations of VaD were reported (Buckwalter et al., 1996).

In the present study, we assessed whether serum levels of TE2, TT, LH, SHBG, calculated BE2 and calculated BT were altered in VaD patients compared to cognitive normal controls. Furthermore, we investigated the associations between these hormones and cognitive and neuropsychiatric symptoms of VaD.

2. Methods

2.1. Subjects

Consecutive VaD patients and cognitive normal controls were from the baseline stage of the China Cognition and Aging Study (China COAST), which is a longitudinal national study on the mild cognitive impairment (MCI) and dementia based on hospital and community population. The diagnosis of dementia was according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). For all our patients, VaD was a consensus diagnosis made by at least two experienced neurologists. These neurologists made the diagnosis strictly according to the criteria of the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS–AIREN) for probable VaD. For the accuracy of the diagnosis, inter-rater reliability for each test and diagnosis was required to exceed 0.90 with videotaped interviews in the China COAST.

All controls had normal cognitive abilities, assessed by the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating (CDR) scale, and none of them had previous history of neurological disorders.

Subjects with acute illnesses at or within one week of the assessment (Cunningham et al., 2001; Hogervorst, Bandelow, Combrinck, & Smith, 2004) or taking exogenous hormones currently or previously were excluded. None of the subjects was receiving psychotropic medication. All female participants were postmenopausal. Written informed consents were obtained from all participants or their relatives. This study was approved by the Institutional Review Board of Xuan Wu Hospital.

2.2. Assessments

Both cases and controls were asked information on age, years of formal education, height, weight, smoking habits, alcohol intake, and medical histories. The body mass index (BMI) was calculated as weight (kilograms) divided by squared height (meters). The MMSE (Folstein, Folstein, & McHugh, 1975) and CDR (Morris, 1993) were used to assess global cognitive ability and dementia severity. The VaD patients underwent more detailed cognitive tests, including the World Health Organization–University of California – Los Angeles Auditory Verbal Learning Test (WHO–UCLA AVLT) (Sacktor et al., 2006) and the Clock Drawing Test (CDT). The WHO-UCLA AVLT was used to measure verbal memory. In this test, the subjects were asked to recall a 15-word list right after the presentation. This kind of immediate recall was repeated 3 times (maximum score = 45). Thirty minutes later, the subjects completed the long delay free recall (maximum score = 15) and long delay recognition (maximum score = 15). The CDT was used to assess the visuospatial and executive functions. The score ranged from 0 to 3—one point for drawing a correct clock shape, one point for writing all the 12 numbers with the right sequence and putting them in the right position, and one point for placing hands correctly (Nishiwaki et al., 2004).

We used the NPI to determine neuropsychiatric symptoms (Cummings et al., 1994). The frequency (occasionally, 1; often, 2; frequently, 3; and very frequently, 4) and severity (mild, 1; moderate, 2; and severe, 3) of each neuropsychiatric symptom on the NPI were asked. The score of each symptom was calculated as the product of the frequency and severity.

2.3. Hormones

A non-fasting blood sample of each subject was collected and the serum was kept at −80 °C until analyzed. An electrochemiluminescence immunoassay (cobas e 601, Roche Diagnostics GmbH, Mannheim, Germany) was used to measure serum levels of TE2, TT, LH, and SHBG. The detection limit of estradiol was 18.4 pmol/L. The intra-assay coefficient of variation (CV) at 130 pmol/L was 3.3%, and interassay CV at 120 pmol/L was 4.7%. The measuring range was 0.020–15.0 ng/mL for testosterone. The intra-assay CV was 2.7% at 0.55 ng/mL and 2.1% at 5.89 ng/mL; the interassay CV was 5.6% at 0.48 ng/mL and 2.5% at 5.43 ng/mL. The detection limit of LH was 0.100 mIU/mL. The intra-assay CVs at 6.15 mIU/mL and 92.2 mIU/mL were 1.2% and 0.9%, respectively, and the interassay CVs at 5.81 mIU/mL and 89.1 mIU/mL were 2.0% and 1.6%, respectively. The measuring range of SHBG was 0.350–200 nmol/L. The intra-assay CV was 1.1% at low levels and 1.7% at high levels; the interassay CV was 1.8% at low levels and 4.0% at high levels. The levels of BE2 and BT were calculated on the basis of TE2 or TT and SHBG levels using the methods described previously (van den Beld, de Jong, Grobbee, Pols, & Lamberts, 2000; Vermeulen, Verdonck, & Kaufman, 1999). A fixed concentration of 43 g/L of albumin was used.

2.4. Data analysis

To explore the characteristics of our subjects, we used independent sample t-tests for continuous data and χ^2 tests for dichotomous variables (Fisher's exact tests if needed). For comparisons of sex hormone levels, a linear regression model was constructed for each hormone. The levels of each hormone and disease status were added to regression models as dependent and independent variables, respectively, and were adjusted for age, BMI, and education. Log transformation of each hormone was used in all regression models. We analyzed the correlations between hormone levels and the scores of cognitive tests of VaD patients by Spearmen tests. We conducted partial correlation analyses between logs of hormones levels and cognitive test scores, controlling for age, education, BMI, and dementia severity. Then, we explored the associations between hormone levels and neuropsychiatric symptoms among VaD patients. The correlations between hormone levels and scores of neuropsychiatric symptoms were assessed by Spearman tests. The logistic regression analyses were performed to examine the associations between hormones and individual neuropsychiatric symptom. The levels and the quartiles of each hormone were added to regression models as independent variables separately and were adjusted for age, education, BMI, and dementia severity. In the present study, all the analyses were conducted in men and women separately with the same methods. A p-value < 0.05 was regarded as statistically significant.

3. Results

3.1. Subjects' characteristics

A total of 87 VaD patients (male = 56 and female = 31) and 110 normal controls (male = 65 and female = 45) were included. The characteristics of our subjects are presented in Table 1. The