MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2013; 19: 681-689
DOI: 10.12659/MSM.889110

Received: 2013.03.03
Accepted: 2013.07.18
Published: 2013.08.19

Plasma cortisol in Alzheimer's disease with or without depressive symptoms

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEF Martina Zvěřová
ABCDEF Zdeněk Fišar
ABE Roman Jirák
ABE Eva Kitzlerová
DE Jana Hroudová
AEG Jiří Raboch

Department of Psychiatry, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic

Corresponding Author: Zdeněk Fišar, e-mail: zfisar@lf1.cuni.cz

Source of support: This research was supported by project MSM0021620849 given by Ministry of Education, Youth and Sports, by project PRVOUK-P26/LF1/4 given by Charles University in Prague, by grant 41310 given by Grant Agency of Charles University, and by grant MH CZ – DRO VFN64165 given by General Teaching Hospital in Prague, Czech Republic

Background: Cortisol is presumed to be a risk factor for stress- and age-related disorders, such as depressive disorder and Alzheimer's disease (AD). The aim of this study was to investigate the association of plasma cortisol concentration with AD in presence or absence of comorbid depressive symptoms.

Material/Methods: Plasma cortisol concentration was measured in 80 AD patients (35 of them with depressive symptoms), 27 elderly depressive patients without AD, and 37 elderly controls.

Results: Compared to controls, a significant increase of mean plasma cortisol was found in AD patients but not in depressive patients. Plasma cortisol was positively correlated with cognitive impairment in AD patients. We confirmed a U-shaped association between plasma cortisol and major depression and a linear association between plasma cortisol and AD without depressive symptoms. Significantly increased relative risk of disease in people with high plasma cortisol was found for AD with depressive symptoms and for AD with mild dementia.

Conclusions: Plasma cortisol reflects the degree of cognitive impairment in AD rather than the severity of comorbid depression. We confirmed that both hypercortisolemia and hypocortisolemia are associated with depressive disorder. Significant association between high plasma cortisol and AD was found, supporting the use of high plasma cortisol as a component of a panel of biochemical markers for AD with depressive symptoms as well as AD in the early stage of dementia development.

Key words: cortisol • Alzheimer's disease • depression • cognitive impairment

Full-text PDF: http://www.medscimonit.com/download/index/idArt/889110

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Background

Depressive disorder and Alzheimer's disease (AD) are ranked among the major neuropsychiatric diseases. AD is the most common neurodegenerative disease, characterized by progressive patterns of cognitive and functional impairments; depressive state in AD escalates the pre-existing suffering of patients. Depression is one of the most frequent psychiatric complications of AD, affecting as many as 50% of patients [1–4]. A link between AD and depression could create hypothalamic-pituitary-adrenal (HPA) axis overdrive, neuroinflammatory mechanisms induced by stress, decreased serotonin levels, and disturbances in many other signaling pathways [5,6].

Major depressive disorder is associated with changes in endocrine and metabolic factors, including monoamine deficits, HPA axis dysfunctions, and inflammatory and neurodegenerative alterations [7,8]. Excessive activation of the HPA axis was observed in approximately half of individuals with depression, which results in increased release of corticotrophin-releasing hormone and, in some cases, sustained elevation of cortisol [9–11]. Mean cortisol concentrations were found to be higher in women than in men, and plasma cortisol concentrations in men and women showed a parallel increase with aging [12–14]. Measurement of salivary, urinary, or serum cortisol levels reveal that depression is associated with hypercortisolemia in older depressed subjects [15–20]. In contrast, other data indicate that hyposecretion of cortisol in elderly patients may be a feature of chronic depressive episodes, especially in males [21]. Thus, in older people, depression is associated with an imbalance of the stress system, resulting in either hypocortisolemia or hypercortisolemia, depending on specific patient characteristics. Hypo- and hypercortisolemic depression may represent different subtypes of depression [22]. The finding that memory retrieval is impaired at very low and very high cortisol levels, but not at intermediate levels, indicates that both low and high cortisol concentrations may participate in the same pathophysiology of the disease [23,24]. A relationship between morning basal serum cortisol, as a measure of HPA axis reactivity, and somatoform dissociative symptoms in unipolar depressive patients was also described [25].

AD is associated with formation of neuritic plaques composed of amyloid-β (Aβ) oligomers and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau protein. However, a growing body of evidence shows that other factors could participate in the pathophysiology of AD [26,27]. Cortisol plasma concentration was found to be increased in AD; nevertheless, the role of cortisol in the pathogenesis of AD remains the subject of controversy [28]. In AD subjects who had higher cortisol levels in the early stage of the disease, an accelerated progression of the disease was observed [29]. Hypercortisolemia in AD appears to be related to the clinical progression of the disease, but not to aging or length of survival [30]. It was confirmed that higher levels of cortisol are not associated with cognitive decline in older persons over a period of 6 years [31]. However, elevated basal cortisol level predicted lower hippocampal volume and cognitive decline in Alzheimer's disease over a 2-year follow-up period [32]. Cortisol levels in AD patients seem to be of prognostic relevance; the most severely demented patients had the highest cortisol concentrations [33], and increased cortisol plasma levels have been associated with more rapid disease progression in AD subjects [34]. However, a large prospective study did not confirm the relation between serum levels of cortisol and the risk of developing dementia or AD, which suggests that morning serum cortisol is not a causal factor in the development of dementia [35]. It was concluded that dysregulation of the HPA axis in AD seems to be a consequence rather than a cause of AD [36]; this was supported by observation that improvement of cognitive function was associated with decreased saliva cortisol [37]. Nevertheless, significantly increased cortisol was included in a biomarker panel for diagnosis of AD [38].

There is an association between depression and dementia [5,39]. Alteration in glucocorticoid steroids and hippocampal atrophy is a link between depression and onset of dementia. Depression with dementia appeared to lower performance on cognitive tests [40] and treatment of depression led to improved test performance [41]. Recently, it has been suggested that major depression could serve as a risk factor for developing AD – patients suffering from lifetime depression have a 2-fold higher chance of developing AD and exhibiting more AD-related neuropathology [5,42]. The role of depression in AD is likely to involve genetic vulnerability, brain damage, and possibly psychological reaction to cognitive decline [2,43]. Cerebrospinal fluid cortisol levels were no higher in depressed than in non-depressed AD patients [44].

The nature of the association between late-life depression and risk of AD is unclear. Although the stress and HPA axis activity participate in the onset and progression of both depressive disorder and AD, it is not known if the pathophysiology of depression in AD is the same as major depressive disorder without AD [45]. Thus, there are important reasons for research on cortisol concentrations in depression, AD, and depressive state in AD. We aimed to investigate the association between plasma cortisol concentration and depressive disorder and AD. Moreover, we analyzed the association of high plasma cortisol with relative risk of AD.

Material and Methods

Subjects

Patients with diagnosis of depressive disorder and patients with diagnosis of AD were recruited from the Department of

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Psychiatry of the First Faculty of Medicine of Charles University in Prague and General University Hospital in Prague. The patients were asked to complete a data set relating to medical history, personal habits, and use of medication.

Inclusion criteria for AD patients were: age >50 years; diagnosis of probable AD according to NINCDS-ADRDA Alzheimer's Criteria; brain imaging (computed tomography or magnetic resonance imaging) showing cortico-subcortical atrophy (atrophy in the hippocampus and temporal lobe); no serious unstable somatic disease and no alcohol abuse; brain imaging excluding any other organic brain lesions (vascular changes, intracranial hemorrhage, etc.). Other causes of dementia were excluded, including pseudo-dementia. Participants did not use oral glucocorticoids, sex steroids, or mineralocorticoids. Standard biochemical survey was performed and persons with pathological levels of minerals, urea, or creatinine were not included. The Mini-Mental State Examination (MMSE) was used to screen for global cognitive impairment in AD patients. Depressive symptoms, which are included in behavioral and psychological symptoms of AD dementia, were assessed us the Geriatric Depression Scale (GDS), designed specifically for rating depression in the elderly [46].

Inclusion criteria for depressive subjects were: age above 50 years, with depressive episode without psychotic symptoms, and with single or recurrent depressive episode. Diagnoses of current depressive episode (F32) or recurrent depressive episode (F33) were confirmed by structured clinical interview for ICD 10. Serious somatic disease or chronic somatic pharmacotherapy was not present; patients were without organic brain disease, without cognitive impairment, and without abuse of psychoactive substances. Severity of depression was assessed using the 21-item Hamilton Rating Scale for Depression (HRSD-21) and the Clinical Global Impression – Severity Scale (CGI-S). Included participants had to have a score greater than 10 on the HRSD and a score of 2 or more on the CGI-S. A negative screen for bipolar disorder was found for all tested subjects using the mood disorder questionnaire (MDQ) [47].

The control group consisted of normal healthy volunteers over 50 years old. To minimize age-related changes in life-style of control subjects, actively employed persons and participants of in the University of the Third Age were accepted as controls. Controls were non-demented, non-depressed, and without any organic brain disorders; they underwent a psychiatric examination and brain imaging in the same way as AD patients.

The study was carried out according to the principles expressed in the Declaration of Helsinki and the study protocol was approved by the Ethics Review Board of the First Faculty of Medicine of Charles University in Prague and General University Hospital in Prague. After completed description of the study to the subjects, written informed consent was obtained.

Plasma cortisol measurement

Fasting blood samples were collected by venipuncture between 7:00 and 8:00 am (at least 1 h after awakening) for determination of total plasma cortisol. Vacutainer® blood collection tubes were used, with EDTA as anticoagulant. Plasma was separated immediately after blood taking and samples were stored at –70°C until the time of analysis. Quantitative determination of cortisol in plasma was performed by competitive immunoassay using direct chemiluminescent technology. Centaur Cortisol reagent kit (Siemens Healthcare Diagnostics Inc., Tarrytown, USA) and ADVIA Centaur analyzer (Siemens Healthcare Diagnostics Inc., Tarrytown, USA) were used; the cortisol assay used has an analytical sensitivity of 20 nmol/L, the inter-assay coefficient of variation was <10%, and intra-assay coefficient of variation was 7%. None of the samples had concentrations of cortisol below the lower detection limit.

Data analysis

Statistical analyses were performed using the data analysis software system STATISTICA (version 10.0, StatSoft, Inc., Tulsa, OK, USA). The hypothesis that plasma cortisol concentrations are normally distributed was tested by the Shapiro-Wilk W test. All data presented are expressed as the mean ± standard deviation (SD). The "General Linear Model" module was used to analyze all designs, including those that can be handled by the Analysis of Variance (ANOVA), regression, or Analysis of Covariance (ANCOVA) methods of analysis, and post-hoc comparison between means. Another way of looking at the unique contributions of each independent variable to the prediction of plasma cortisol concentration was to compute the partial correlations (i.e., correlations between the respective independent variable adjusted by all other variables, and the plasma cortisol adjusted by all other variables).

The "high cortisol group" was operationally defined by plasma cortisol concentration exceeding the normal mean value plus 2 SD [48], corresponding to specificity greater than 0.97 for controls. Two-way contingency table analysis was used to estimate the association of cortisol status with AD and/or depression (i.e., odds ratio [OR], relative risk [RR], and sensitivity were calculated with 95% confidence intervals [CI]).

Results

Participants were grouped according to diagnosis into 3 groups: patients with AD (*N*=80), patients with depressive disorder (*N*=27), and controls (*N*=37). AD patients were subgrouped to those with marked depressive symptoms (GDS ≥7, *N*=35) and without marked depressive symptoms (GDS <7, *N*=45). Demographic data are summarized in Table 1 and

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

clinical evaluation and plasma cortisol concentrations are shown in Table 2.

First, data normality was tested. The hypothesis that distribution of plasma cortisol concentrations is normal distribution was not rejected by the Shapiro-Wilk W test for AD patients, depressive patients, and controls. Thus, parametric statistics were used for subsequent data evaluation.

Second, control for sex was performed. While slightly higher mean plasma cortisol concentrations were found in women compared to men in all tested groups, statistical analysis (ANOVA and post-hoc Scheffé test) did not discover any significant difference. Post-hoc *p*-levels for the Scheffé test were 0.063, 0.112, 0.307, 0.802, and 0.067 for AD, AD with depression, AD without depression, depressive disorder, and control, respectively. Thus, data from women were evaluated together with data from men.

Compared to controls, AD patients had significantly higher mean plasma cortisol concentration (p=0.021), as did subgroups of AD patients with depressive symptoms (p=0.044), but not in AD without depression or in non-AD depressed patients (Table 2). Significantly higher plasma cortisol was also found in AD patients compared to depressive patients (p=0.042).

General linear models were used for investigation of significant interaction effects for plasma cortisol and both categorical and continuous predictor variables. Association of plasma cortisol with MMSE and GDS was studied in AD patients. Association of plasma cortisol with HRSD score and CGI-S score was assayed in patients with depressive disorder (without

Table 1. Demographic data of study participants.

Characteristic Mean ±SD (range)	Alzheimer's disease			Depressive disorder	Control
	All	With depression	Without depression		
Age (years)	***75.6±7.7 (56–91)	***76.1±6.8 (62–87)	***75.1±8.4 (56–91)	59.1±5.1 (53–69)	63.2±7.6 (51–77)
Schooling (years)	13.9±2.8 (8–18)	14.1±3.0 (8–18)	13.8±2.7 (9–18)	13.3±2 (9–18)	13.9±2.0 (12–18)
BMI (kg/m^2)	**24.0±3.4 (18.7–36.3)	25.5±4.0 (18.8–36.3)	**23.0±2.4 (19.6–30.2)	26.3±4.2 (18.7–30.2)	28.6±3.8 (23.7–33.9)
N (women/men)	80 (49/31)	35 (21/14)	45 (28/17)	27 (21/6)	37 (29/8)

ANOVA and post-hoc Scheffé test were used to determine indicated *p*-level compared to controls; **p<0.01, ***p<0.001; SD – standard deviation; BMI – body mass index

Table 2. Clinical evaluation of participants and plasma cortisol concentrations.

Characteristic Mean ±SD (range)	Alzheimer's disease			Depressive disorder	Control
	All	With depression	Without depression		
GDS	***6.0±3.7 (1–13)	***9.7±2.1 (7–13)	***3.1±1.3 (1–6)	–	0.3±0.8 (0–4)
MMSE	***19.2±6.8 (1–25)	***19.8±6.5 (1–25)	***18.8±7.1 (2–25)	29.5±0.9 (27–30)	29.4±1.0 (26–30)
HRSD	–	–	–	24.1±7.4 (11–39)	–
CGI-S	–	–	–	4.4±1.0 (2–6)	–
Cortisol (nmol/L)	*556±135 (253–876)	*572±150 (253–840)	543±123 (263–876)	478±170 (179–786)	479±112 (289–709)
N	80	35	45	27	37

ANOVA and post-hoc Scheffé test were used to determine indicated *p*-level; *p<0.05, ***p<0.001; GDS – Geriatric Depression Scale; MMSE – Mini-Mental State Examination; HRSD – 21-item Hamilton Rating Scale for Depression; CGI-S – Clinical Global Impression – Severity scale.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 3. Relationships between plasma cortisol concentration, Mini-Mental State Examination (MMSE) score and Geriatric Depression Scale (GDS) after nonadjusted and adjusted analysis in patients with Alzheimer's disease (AD).

Model	Variable	All AD			AD with depression			AD without depression		
		Intercept	MMSE	GDS	Intercept	MMSE	GDS	Intercept	MMSE	GDS
A	Regression coefficient	613	–3.7	2.2	669	–1.7	–6.6	681	*–5.8	–9.6
	p value	0.000	0.096	0.586	0.001	0.696	0.621	0.000	0.023	0.476
	Partial correlation		–0.188	0.062		–0.069	–0.087		*–0.341	–0.110
B	Regression coefficient	513	–3.6	2.0	388	–0.4	–4.7	617	*–6.0	–13.1
	p value	0.002	0.109	0.615	0.343	0.935	0.722	0.001	0.022	0.339
	Partial correlation		–0.183	0.058		–0.014	–0.065		*–0.352	–0.151
C	Regression coefficient	603	*–5.1	2.9	506	–3.8	–12.3	934	**–7.5	–11.1
	p value	0.010	0.023	0.491	0.287	0.393	0.331	0.006	0.008	0.417
	Partial correlation		*–0.264	0.081		–0.164	–0.187		**–0.414	–0.131

Model A: Unadjusted; Model B: Adjusted for age and sex; Model C: Adjusted for age, sex, years of schooling, and body mass index.

dementia). Control for age, sex, years of schooling, and body mass index (BMI) was performed for all groups. Partial correlation (a correlation between 2 variables that remains after controlling for 1 or more other variables) was also calculated.

Multiple regression did not discover any significant regression coefficients in the group of depressive patients (i.e., none of the independent variables contributes significantly to the prediction of plasma cortisol in this group of participants). In the control group we found significant association between plasma cortisol and age only, with partial correlation adjusted for sex equal to 0.419. However, we found a significant association of plasma cortisol with MMSE score in AD patients (Table 3). MMSE was identified as the most important predictor of plasma cortisol both in the whole group of AD patients (after adjustment for age, sex, years of schooling, and BMI) and in the subgroup of AD patients without depressive symptoms (apart from adjustment). After adjustment for confounding, *p* values were unchanged or slightly decreased. The relation between plasma cortisol in AD patients and MMSE and/or GDS was documented by partial correlation and regression coefficients of multiple linear regression analysis for model unadjusted, adjusted for age and sex, and adjusted for age, sex, BMI, and years of schooling (Table 3). The dependence of plasma cortisol on MMSE score in AD patients is shown in Figure 1.

It was previously found that, in older people, the association between cortisol and depression is U-shaped [22]. Higher standard deviation and range of plasma cortisol concentrations in non-AD depressive patients (Table 2) indicates that both low and high levels of cortisol are associated with depression. Quartiles (i.e., values that divide the data set into 4 equal groups, each representing a fourth of the population being sampled), were

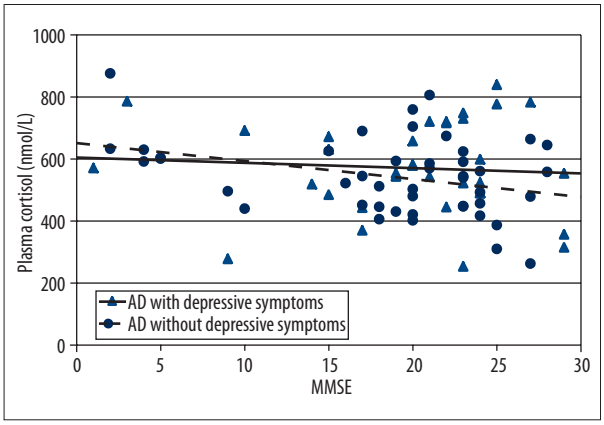

Figure 1. The linear regression plot of a plasma cortisol in patients with Alzheimer's disease (AD) against Mini-Mental State Examination (MMSE) score. Comorbid depressive symptoms were assessed by Geriatric Depression Scale (GDS) and regression lines of unadjusted model are shown for AD patients with marked depressive symptoms (GDS ≥7) and without them (GDS <7).

determined for the control group and they were used for data separation in the group of AD or depressive patients. Relative number of patients in each quartile is displayed on Figure 2, which shows that the number of patients with depressive disorder increases at both ends of the plasma cortisol spectrum. Thus, we confirmed a U-shaped association between plasma cortisol and major depression. In contrast, AD patients without depressive symptoms display a linear increase of the relative number of patients with increased plasma cortisol concentration. Distribution of relative number of AD patients with depressive symptoms is more complex and may be due to superposition of linear and U-shaped course.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

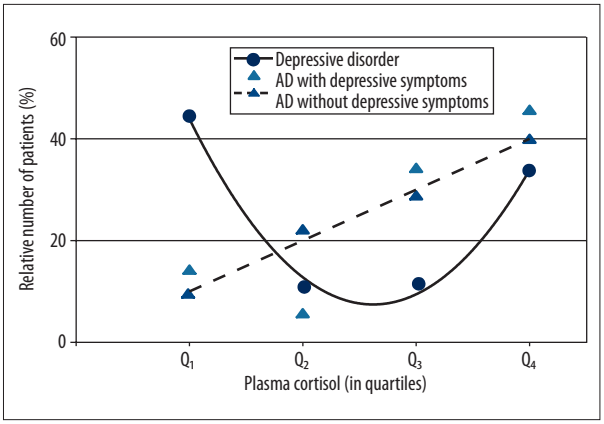

Figure 2. Distribution of relative number of patients with depressive disorder, Alzheimer's disease (AD) with depressive symptoms, and AD without depressive symptoms according to plasma cortisol concentration. Following quartiles determined for the control group were used: Q_1=cortisol ≤404, Q_2=404< cortisol ≤465, Q_3=465< cortisol ≤573, Q_4= cortisol >573 nmol/L.

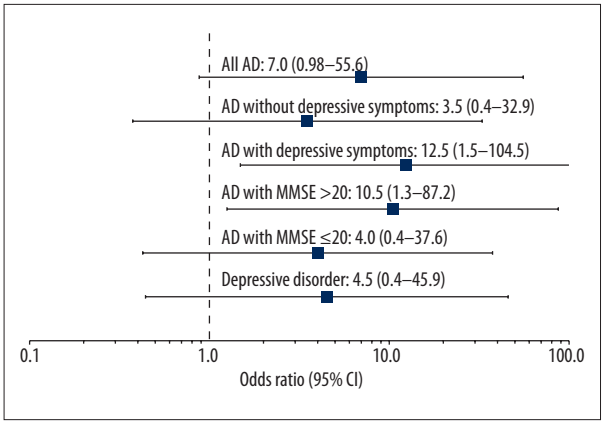

Figure 3. Association of between high plasma cortisol (>700 nmol/L) and Alzheimer's disease (AD), AD without depressive symptoms, AD with depressive symptoms, AD with mild dementia and Mini-Mental State Examination (MMSE) score >20, AD with moderate to severe dementia and MMSE ≤20, and depressive disorder. Significant association was found between high cortisol and AD with depressive symptoms or AD with mild dementia.

To express the utility of increased plasma cortisol concentration as part of a panel of biological markers of the disease, we dichotomized data to those with "normal" and "high" plasma cortisol. We chose 700 nmol/L plasma cortisol concentration, which approximately corresponds to the mean value of the control group increased by 2 SD, as the lower limit for "high" cortisol concentration. In AD patients, the high cortisol concentration (>700 nmol/L) was found in 16.3% (*N*=13) of the whole group (*N*=80), 25.7% (*N*=9) of those with depressive symptoms (*N*=35), 8.9% (*N*=4) of those without depressive symptoms (*N*=45), 22.5% (*N*=9) of those with MMSE>20 and mild dementia (*N*=40), and 10.0% (*N*=4) of those with MMSE ≤20 and moderate to severe dementia (*N*=40). Only 11.1% (*N*=3) of depressive patients (*N*=27) and 2.7% (*N*=1) of controls (*N*=37) fell into high plasma cortisol subgroups. Mean MMSE scores were not significantly different in AD patients with high and normal plasma cortisol.

The following relationships were analyzed using the odds ratio, relative risk, sensitivity, and specificity (with 95% confidence intervals) in the subjects with high plasma cortisol concentration: (1) AD among subjects with AD and control subjects; (2) AD without depressive symptoms (GDS <7) among these and control subjects; (3) AD with depressive symptoms (GDS ≥7) among these and control subjects; (4) AD with MMSE >20 among these and controls; (5) AD with MMSE ≤20 among these and controls; and (6) Depressive patients among subjects with depressive disorder and control subjects (Figure 3). Test sensitivity was very low (below 0.30) for both AD and depressive disorder. Specificity of 0.97 was calculated from values for controls. Significantly increased relative risk (*RR*) of disease in persons with high plasma cortisol was found in AD patients (*RR*=1.43, 95% CI 1.16–1.74), in the subgroup of AD patients with marked depressive symptoms (*RR*=2.15, 95% CI 1.50–3.07) and in AD patients with mild dementia and MMSE >20 (*RR*=1.95, 95% CI 1.40–2.71).

Discussion

This study was designed to analyze an association of AD and/or depression with plasma cortisol concentration. Multiple linear regression analysis was applied to learn which of the independent variables contributes most to the prediction of plasma cortisol concentration. We examined the regression coefficients to determine the strength of the relationship between plasma cortisol and the continuous determinants. Our preliminary data support the role of cortisol as part of a panel of biomarkers for depression [7] and age-related neurodegenerative diseases such as AD [38].

Previously, it was found that morning cortisol levels increased 30% between the ages of 40 and 80 years in a cross-sectional study of more than 2000 randomly selected Canadian men [49], concordant with the 20% elevation from age 50–89 years observed in another large study [14]. In our study, we confirmed significant positive partial correlation between plasma cortisol and age in the control group (51–77 years old). However, we did not find significant association of morning plasma cortisol concentration with age in AD (56–91 years old) or in depressive patients (53–69 years old), probably due to effects of the disease on plasma cortisol. Age adjustment was performed in data analysis to remove the confounding effect of age.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

We found slightly higher mean plasma cortisol concentrations in women compared to men in all tested groups; however, statistical analysis did not confirm any significant difference. This enabled us to analyze data from women together with data from men.

Mean plasma cortisol concentration was not increased in depressive disorder compared to controls (Table 2). Normalization of HPA axis hyperactivity after treatment with antidepressants [50] and association of both hypo- and hypercortisolemia with depressive disorder (Figure 2) may play a role in this. Our results supported previous finding that elevation of cortisol occurs only in some individuals with depression and that there is U-shaped association between plasma cortisol and major depression [9,22].

We found significantly increased mean cortisol concentration in AD patients (+16.1%) and in their subgroups compared to healthy controls, similar to the findings of Laske et al. [51] (Table 2). Plasma cortisol was increased by 19.4% in AD with depressive symptoms and by 13.4% in AD without depression, but the difference was not statistically significant. Our data confirmed that there is a continuously increasing distribution of number of AD patients without depressive symptoms with increasing plasma cortisol (Figure 2). These results indicate different roles of cortisol in AD and in depressive disorder.

We confirmed that depression is frequently comorbid with AD; 44% of AD patients also showed marked depressive symptoms. Significant association was found between plasma cortisol and MMSE in the whole group of AD patients after adjustment for age, sex, years of schooling, and BMI, and in the subgroup of AD patients without depressive symptoms apart from adjustment (Table 3). Because GSD score was not significantly associated with plasma cortisol, we suppose that plasma cortisol is associated with degree of cognitive impairment in AD rather than with comorbid depressive symptoms.

Significantly increased odds ratio or relative risk of disease in subjects with high plasma cortisol was found in AD, in AD with mild dementia, and in AD with depressive symptoms especially, but not in AD without depressive symptoms or in AD with moderate to severe dementia (Figure 3). These results partially support previous findings that there is no simple association between plasma cortisol levels and clinical and cognitive assessments obtained at the single assessment closest in time to the plasma collection [34] and that depressive symptoms may affect plasma cortisol in AD.

The strength of this study is the very rigorous diagnosis and clinical evaluation of AD and depressive patients. The study has several limitations. First, mean age was higher in AD patients compared to controls or patients with depressive disorder, but we believe that it is not serious problem, because we did not find significant association of plasma cortisol with age in AD patients or in depressive patients. The increase of about 5% of plasma cortisol concentration could be expected for the 12-year difference of mean ages in our study [14,49]. We think that adjustment for age in statistical data analysis is sufficient to correct this discrepancy. Second, total plasma cortisol does not represent the bioactive portion of cortisol that is available to bind to receptors [22,52]; thus, total plasma cortisol does not represent the complete picture of HPA axis activity. However, this is not a problem, because hypercortisolemia in severe depression appears to be driven largely by increased basal cortisol secretion that is dissociated from stimulation by adrenocorticotropic hormone [48]. Third, blood samples were collected only once; thus, cortisol concentrations may be influenced by acute effects. This was because our study was designed to determine an association of single plasma cortisol measurement with clinical assessment and/or to evaluate usefulness of once-measured high plasma cortisol as part of a panel of biological markers of the disease. Nevertheless, blood taking was performed at least 1 hour after awakening to avoid the morning peak of cortisol. Another possible limitation is interference by current pharmacotherapy of depressed or AD patients. AD patients were treated by reversible acetylcholinesterase inhibitors and/or by *N*-methyl-D-aspartate (NMDA) receptor antagonists, and by other drugs according to their somatic illnesses; those with co-morbid depression were usually treated with antidepressants as well. However, responders using oral glucocorticoids, sex steroids, or mineralocorticoids were excluded from the study to minimize the confounding effect of pharmacotherapy on plasma cortisol.

Most of the AD patients in our study were in early stages of the illness. We suppose that some of these AD patients with current mild dementia will be repeatedly tested in future to obtain data for longitudinal study of cortisol levels during progression of AD.

Evidence has been accumulating about the role of stress and HPA axis activity as an important challenge to the onset and progression of depressive disorder and AD. The hippocampus, one of the areas of the brain damaged during both depressive disorder and AD, was recognized as a target of neurotransmitters, cytokines, and stress hormones, including cortisol. Our preliminary study confirms that increased plasma cortisol in AD is relatively little affected by comorbid depressive symptoms and that there is an association between plasma cortisol concentration and cognitive impairment in AD without depressive symptoms. However, much additional work has to be done to establish plasma cortisol as a reliable biomarker. Future research evolving from our preliminary work may include multiple blood sampling from each subject, simultaneous measurement of several biomarkers of AD and/or depressive disorder,

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

and a longitudinal study. Such research could contribute to the debate on whether depression is a risk for AD and vice-versa, and whether cortisol plays a causal role in this relationship.

Conclusions

Mean plasma cortisol concentrations were increased in AD compared to controls; the increase was only slightly higher in AD with depression compared to AD without depression. Mean plasma cortisol did not change in depressive disorder without AD and was not correlated with severity of depression. Plasma cortisol reflects MMSE-assessed degree of cognitive impairment in AD rather than the severity of comorbid depression. We confirmed a U-shaped association between plasma cortisol and major depression – both low and high concentrations of cortisol are associated with increased prevalence of depressive disorder in elderly people. In contrast, we discovered a linear increase in distribution of AD patients without depressive symptoms with higher plasma cortisol, indicating that hypercortisolemia, but not hypocortisolemia, is associated with AD. A significantly increased relative risk of the disease in people with single measured high plasma cortisol was found in the subgroup of AD patients with depressive symptoms and in AD patients with mild dementia. High plasma cortisol may be an important component of a panel of biochemical markers of AD with comorbid depression.

Conflict of interests

None of the authors have any conflicts of interest pertaining to this article.

References:

1. Migliorelli R, Tesón A, Sabe L et al: Prevalence and correlates of dysthymia and major depression among patients with Alzheimer's disease. Am J Psychiatry, 1995; 152: 37–44
2. Lyketsos CG, Olin J: Depression in Alzheimer's disease: overview and treatment. Biol Psychiatry, 2002; 52: 243–52
3. Starkstein SE, Jorge R, Mizrahi R, Robinson RG: The construct of minor and major depression in Alzheimer's disease. Am J Psychiatry, 2005; 162: 2086–93
4. Lyketsos CG, Carrillo MC, Ryan JM et al: Neuropsychiatric symptoms in Alzheimer's disease. Alzheimers Dement, 2011; 7: 532–39
5. Sierksma AS, van den Hove DL, Steinbusch HW, Prickaerts J: Major depression, cognitive dysfunction and Alzheimer's disease: is there a link? Eur J Pharmacol, 2010; 626: 72–82
6. Ricci S, Fuso A, Ippoliti F, Businaro R: Stress-induced cytokines and neuronal dysfunction in Alzheimer's disease. J Alzheimers Dis, 2012; 28: 11–24
7. Schmidt HD, Shelton RC, Duman RS: Functional biomarkers of depression: diagnosis, treatment, and pathophysiology. Neuropsychopharmacology, 2011; 36: 2375–94
8. Maes M, Fišar Z, Medina M et al: New drug targets in depression: inflammatory, cell-mediated immune, oxidative and nitrosative stress, mitochondrial, antioxidant, and neuroprogressive pathways. And new drug candidates – Nrf2 activators and GSK-3 inhibitors. Inflammopharmacology, 2012; 20: 127–50
9. Bao AM, Meynen G, Swaab DF: The stress system in depression and neurodegeneration: focus on the human hypothalamus. Brain Res Rev, 2008; 57: 531–53
10. Gold PW, Chrousos GP: Organization of the stress system and its dysregulation in melancholic and atypical depression: high *vs.* low CRH/NE states. Mol Psychiatry, 2002; 7: 254–75
11. Holsboer F: Stress, hypercortisolism and corticosteroid receptors in depression: implications for therapy. J Affect Disord, 2001; 62: 77–91
12. Otte C, Hart S, Neylan TC et al: A meta-analysis of cortisol response to challenge in human aging: importance of gender. Psychoneuroendocrinology, 2005; 30: 80–91
13. Van Cauter E, Leproult R, Kupfer DJ: Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. J Clin Endocrinol Metab, 1996; 81: 2468–73
14. Laughlin GA, Barrett-Connor E: Sexual dimorphism in the influence of advanced aging on adrenal hormone levels: the Rancho Bernardo Study. J Clin Endocrinol Metab, 2000; 85: 3561–68
15. Halbreich U, Asnis GM, Zumoff B et al: Effect of age and sex on cortisol secretion in depressives and normals. Psychiatry Res, 1984; 13: 221–29
16. Gotthardt U, Schweiger U, Fahrenberg J et al: Cortisol, ACTH, and cardiovascular response to a cognitive challenge paradigm in aging and depression. Am J Physiol, 1995; 268: R865–73
17. O'Brien JT, Lloyd A, McKeith I et al: A longitudinal study of hippocampal volume, cortisol levels, and cognition in older depressed subjects. Am J Psychiatry, 2004; 161: 2081–90
18. Hinkelmann K, Moritz S, Botzenhardt J et al: Cognitive impairment in major depression: association with salivary cortisol. Biol Psychiatry, 2009; 66: 879–85
19. Köhler S, Thomas AJ, Lloyd A et al: White matter hyperintensities, cortisol levels, brain atrophy and continuing cognitive deficits in late-life depression. Br J Psychiatry, 2010; 196: 143–49
20. ó Hartaigh B, Loerbroks A, Thomas GN, et al: Age-dependent and -independent associations between depression, anxiety, DHEAS, and cortisol: from the MIPH Industrial Cohort Studies (MICS). Psychoneuroendocrinology, 2012; 37: 929–36
21. Oldehinkel AJ, van den Berg MD, Flentge F et al: Urinary free cortisol excretion in elderly persons with minor and major depression. Psychiatry Res, 2001; 104: 39–47
22. Bremmer MA, Deeg DJ, Beekman AT et al: Major depression in late life is associated with both hypo- and hypercortisolemia. Biol Psychiatry, 2007; 62: 479–86
23. Rimmele U, Besedovsky L, Lange T, Born J: Blocking mineralocorticoid receptors impairs, blocking glucocorticoid receptors enhances memory retrieval in humans. Neuropsychopharmacology, 2013; 38: 884–94
24. Schilling TM, Kölsch M, Larra MF et al: For whom the bell (curve) tolls: Cortisol rapidly affects memory retrieval by an inverted U-shaped dose-response relationship. Psychoneuroendocrinology, 2013; pii: S0306-4530(13)00005-X
25. Bob P, Fedor-Freybergh P, Jasova D et al: Dissociative symptoms and neuroendocrine dysregulation in depression. Med Sci Monit, 2008; 14(10): CR499–504
26. Fjell AM, Walhovd KB: Neuroimaging results impose new views on Alzheimer's disease – the role of amyloid revised. Mol Neurobiol, 2012; 45: 153–72
27. Zimny A, Bladowska J, Neska M et al: Quantitative MR evaluation of atrophy, as well as perfusion and diffusion alterations within hippocampi in patients with Alzheimer's disease and mild cognitive impairment. Med Sci Monit, 2013; 19: 86–94
28. Swaab DF, Bao AM, Lucassen PJ: The stress system in the human brain in depression and neurodegeneration. Ageing Res Rev, 2005; 4: 141–94
29. Umegaki H, Ikari H, Nakahata H et al: Plasma cortisol levels in elderly female subjects with Alzheimer's disease: a cross-sectional and longitudinal study. Brain Res, 2000; 881: 241–43.
30. Weiner MF, Vobach S, Olsson K et al: Cortisol secretion and Alzheimer's disease progression. Biol Psychiatry, 1997; 42: 1030–38
31. Comijs HC, Gerritsen L, Penninx BW et al: The association between serum cortisol and cognitive decline in older persons. Am J Geriatr Psychiatry, 2010; 18: 42–50

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

32. Huang CW, Lui CC, Chang WN et al: Elevated basal cortisol level predicts lower hippocampal volume and cognitive decline in Alzheimer's disease. J Clin Neurosci, 2009; 16: 1283–86
33. Davis KL, Davis BM, Greenwald BS et al: Cortisol and Alzheimer's disease, I: Basal studies. Am J Psychiatry, 1986; 143: 300–5
34. Csernansky JG, Dong H, Fagan AM et al: Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia. Am J Psychiatry, 2006; 163: 2164–69
35. Schrijvers EM, Direk N, Koudstaal PJ et al: Associations of serum cortisol with cognitive function and dementia: the Rotterdam Study. J Alzheimers Dis, 2011; 25: 671–77
36. Gil-Bea FJ, Aisa B, Solomon A et al: HPA axis dysregulation associated to apolipoprotein E4 genotype in Alzheimer's disease. J Alzheimers Dis, 2010; 22: 829–38
37. Tanaka M, Ishii A, Yamano E et al: Effect of a human-type communication robot on cognitive function in elderly women living alone. Med Sci Monit, 2012; 18(9): CR550–57
38. Doecke JD, Laws SM, Faux NG et al: Alzheimer's Disease Neuroimaging Initiative; Australian Imaging Biomarker and Lifestyle Research Group: Blood-based protein biomarkers for diagnosis of Alzheimer disease. Arch Neurol, 2012; 69: 1318–25
39. Byers AL, Yaffe K: Depression and risk of developing dementia. Nat Rev Neurol, 2011; 7: 323–31
40. Tanaka M, Ishii A, Yamano E et al: Cognitive dysfunction in elderly females with depressive symptoms. Med Sci Monit, 2012; 18(12): CR706–11
41. Greenwald BS, Kramer-Ginsberg E, Marin DB et al: Dementia with coexistent major depression. Am J Psychiatry, 1989; 146: 1472–78
42. Ownby RL, Crocco E, Acevedo A et al: Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry, 2006; 63: 530–58
43. Lee HB, Lyketsos CG: Depression in Alzheimer's disease: heterogeneity and related issues. Biol Psychiatry, 2003; 54: 353–62
44. Meynen G, Unmehopa UA, Hofman MA et al: Hypothalamic vasopressin and oxytocin mRNA expression in relation to depressive state in Alzheimer's disease: a difference with major depressive disorder. J Neuroendocrinol, 2009; 21: 722–29
45. Yesavage JA, Brink TL, Rose TL et al: Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res, 1982–1983; 17: 37–49
46. Hirschfeld RM: Screening for bipolar disorder. Am J Manag Care, 2007; 13: S164–69
47. Carroll BJ, Iranmanesh A, Keenan DM et al: Pathophysiology of hypercortisolism in depression: pituitary and adrenal responses to low glucocorticoid feedback. Acta Psychiatr Scand, 2012; 125: 478–91
48. Bélanger A, Candas B, Dupont A et al: Changes in serum concentrations of conjugated and unconjugated steroids in 40- to 80-year-old men. J Clin Endocrinol Metab, 1994; 79: 1086–90
49. Schüle C: Neuroendocrinological mechanisms of actions of antidepressant drugs. J Neuroendocrinol, 2007; 19: 213–26
50. Laske C, Stransky E, Fritsche A et al: Inverse association of cortisol serum levels with T-tau, P-tau 181 and P-tau 231 peptide levels and T-tau/Aβ 1-42 ratios in CSF in patients with mild Alzheimer's disease dementia. Eur Arch Psychiatry Clin Neurosci, 2009; 259: 80–85
51. Kumsta R, Entringer S, Hellhammer DH, Wüst S: Cortisol and ACTH responses to psychosocial stress are modulated by corticosteroid binding globulin levels. Psychoneuroendocrinology, 2007; 32: 1153–57

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]