Short communication

Plasma cortisol levels in elderly female subjects with Alzheimer’s disease: a cross-sectional and longitudinal study

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Abstract

We investigated the plasma cortisol levels at a fasting state in elderly female Alzheimer’s disease (AD), vascular dementia (VD), and non-demented subjects ($n=66$, 28 and 21, respectively). Twenty-eight AD subjects were followed for 40 months. The plasma cortisol levels in AD and VD subjects were significantly higher than those of non-demented subjects at baseline. In AD subjects in relatively early stages of the disease [Mini-Mental State Examination (MMSE)], at baseline, high plasma cortisol led to rapid declines in MMSE scores over a 40-month period. © 2000 Elsevier Science B.V. All rights reserved.

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Many past studies have shown that several aspects of neuroendocrine systems are altered in the course of Alzheimer’s disease (AD) [13,14]. Hypercortisolemia is one of the most frequently reported changes [5,6,11]. Sapolsky et al. [7,8] found that aged rats have a decreased number of glucocorticoid receptors and an impaired negative feedback mechanism of glucocorticoid secretion. A high concentration of glucocorticoid receptors exists in the hippocampus, and this brain region is thought to be involved in the negative-feedback mechanism of glucocorticoid secretion. Animal studies have demonstrated that elevated cortisol levels make neurons more vulnerable to several kinds of insults [1,9]. The degeneration of the hippocampus is one of the most notable features of AD pathologies [4]. Based on their findings, Sapolsky and McEwen [10] proposed the glucocorticoid cascade theory. According to this theory, hippocampal cell loss in AD induces hypercortisolemia, which, in turn, acts as a co-factor in further degeneration of the disease process.

In the current study, we report cross-sectional findings of cortisol profiles in AD subjects as compared to those of subjects with vascular dementia (VD) and non-demented controls (ND), and we report the longitudinal findings in AD subjects followed over a 40-month period.

All AD and VD subjects were hospitalized in Fukushimura Hospital in Aichi, Japan. ND subjects lived in a nursing home near Fukushimura Hospital. This study was approved by the Human Subject Review Committee of Fukushimura Hospital. After all of the procedures had been fully explained, written informed consent was obtained from all subjects or their guardians. The subjects were non-smokers, and those who had chronic obstructive pulmonary diseases, diabetes mellitus, neurodegenerative disease, or abnormal thyroid function were excluded. The Diagnostic and Statistical Manual of Mental Disorders Fourth Edition [12] was used to arrive at the diagnoses of AD and VD. Computed tomographies of the brain were performed for all subjects. No subjects in the AD and ND groups had cerebral vascular diseases.

The total number of subjects enrolled in the study was 115 (AD=66, VD=28 and ND=21). The first examination was performed in November 1996, and a follow-up examination was performed 40 months later, in March 2000. The progress of 28 out of 66 AD subjects was followed.

A score for Mini-Mental State Examination (MMSE)
[3], which is a widely used dementia assessment instrument, was obtained from all subjects. The blood samples were collected at 7 a.m. from subjects in a fasting state. The blood samples were kept on ice and cold-centrifuged immediately after collection. The plasma was stored at −70°C until assay. Cortisol and adrenocorticotropic hormone (ACTH) were measured by radioimmunoassay.

Table 1 shows the baseline profiles (November 1996) of all of the subjects enrolled in this study and 28 AD subjects who were followed until March, 2000. The mean age was 82.50 years. The scores of AD subjects and VD subjects were significantly lower than that of ND subjects.

The basal plasma cortisol levels at a fasting state at baseline in the three groups were AD=15.24±3.23 μg/ml, VD=15.19±3.95 μg/ml and ND=12.88±2.77 μg/ml. One way ANOVA shows that plasma cortisol levels have significant differences among the three groups (P=0.0171). Cortisol levels in AD and VD subjects were significantly higher than those in ND subjects, according to Scheffe’s post-hoc test (P=0.0058 and 0.0181, respectively). ACTH levels were not significantly different among these three groups (AD=45.77±24.49 pg/ml, VD=42.07±18.70 pg/ml and ND=46.05±27.69 pg/ml).

The mean scores of MMSEs in the three groups of subjects at baseline were 7.96, 5.29 and 24.52, respectively (Table 1). MMSE scores at baseline were not correlated with baseline cortisol levels in AD subjects (data not shown).

The mean MMSE score of AD subjects who were followed was 7.99±6.52 at baseline and declined to 1.43±0.46. This decline of MMSE score was statistically significant (paired t-test) (P<0.0001). However, the plasma cortisol levels did not change over the 40-month period (15.45±0.53 and 15.45±0.59 μg/ml, respectively).

There was no association between the basal cortisol level and the changes of MMSE scores during the follow-up period in which all subjects were included (Fig. 1A). However, when only the mildly demented subjects with MMSE scores of more than 14 at baseline were analyzed, a significant correlation was observed between the changes in MMSE scores and the basal cortisol level (n=9) (Fig. 1B).

We have demonstrated in the present study that plasma levels of cortisol were significantly higher in both AD and VD subjects than in ND subjects. The levels of ACTH were not significantly different among the three groups, and this is in agreement with previous studies [2,5]. The mechanism of the discrepancy between levels of cortisol and ACTH has yet to be elucidated.

The cortisol levels of AD subjects whose progress was followed did not change significantly over 40 months, while during this period, the MMSE scores of these subjects declined significantly.

Weiner et al. [15] reported a significant correlation between changes in scores of modified ADAS-COG and basal cortisol levels in a similar follow-up study, which investigated the subjects in early stages of AD (mean scores of MMSE=20.0±4.1). In the current study, as shown in Fig. 1A, the basal cortisol level did not predict the decline in MMSE scores when all of the subjects were included. Swanwick et al. [11] suggested that the glucocorticoid cascade theory may be relevant in the early stages of AD progression. As shown in Fig. 1B, when only relatively less demented subjects (MMSE scores were more than 14) were analyzed, statistical analysis showed a significant correlation between the changes in MMSE scores and the basal level of plasma cortisol. The AD subjects who had higher basal levels of plasma cortisol showed greater declines in MMSE scores. This suggests that the plasma cortisol level in a fasting state may predict the progression of AD, at least in moderate stages of the disease.

In summary, we demonstrated the following results in the present study: (1) AD and VD subjects had significantly higher levels of plasma cortisol than ND subjects. (2) The cortisol levels in a fasting state in AD subjects did not change significantly, while the MMSE scores declined significantly over a 40-month period. (3) In AD subjects in relatively early stages of the disease (MMSE≥14) who had higher cortisol levels, an accelerated progression of the disease was observed.

<p>| Table 1 |
| The number, mean age and MMSE scores at baseline of all subjects and AD subjects whose progress was followed |</p>
<table>
<thead>
<tr>
<th>All subjects</th>
<th>AD</th>
<th>VD</th>
<th>ND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>66</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td>Mean age (mean±S.D.)</td>
<td>82.49±7.77</td>
<td>82.86±5.86</td>
<td>82.95±7.77</td>
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<tr>
<td>Mean atrial pressure (mean±S.D.) (mmHg)</td>
<td>92.64±10.99</td>
<td>94.74±10.31</td>
<td>94.56±12.09</td>
</tr>
<tr>
<td>Mean score of MMSE (mean±S.D.)</td>
<td>7.96±6.49</td>
<td>5.29±5.19</td>
<td>24.52±2.86</td>
</tr>
<tr>
<td>Followed subjects</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
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<td></td>
</tr>
<tr>
<td>Mean age (mean±S.D.)</td>
<td>82.49±4.98</td>
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<td></td>
</tr>
<tr>
<td>Mean score of MMSE (mean±S.D.)</td>
<td>7.99±6.52</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fig. 1. (A) Simple regression analysis showed no correlation between plasma cortisol levels and changes in MMSE scores during the follow-up period when analyzed in all the subjects \( (P=0.2433) \). (B) Simple regression analysis showed a significant correlation between plasma cortisol levels and changes in MMSE scores during the follow-up period when analyzed in subjects with relatively mild dementia (MMSE\(\geq14\)) \( (P=0.0307) \).

References


