Increased cerebrospinal fluid cortisol level in Alzheimer’s disease is not related to depression.
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Abstract
Hypothalamo-pituitary-adrenal (HPA)-axis hyperactivity is well established in a large proportion of both Alzheimer’s disease (AD) patients and major depressive disorder (MDD) patients, resulting in e.g. increased cerebrospinal fluid (CSF) cortisol levels. We hypothesized that HPA-axis activity in depressed AD patients is even more increased than in non-depressed AD patients, resulting in higher CSF cortisol levels. Cortisol levels were measured in post mortem CSF of depressed and non-depressed AD patients and in controls. Cortisol levels in AD patients were more than double those of controls, while no significant differences were found between depressed and non-depressed AD patients. These results suggest a different pathogenetic mechanism in depression in AD than in MDD.

Introduction
Depression occurs in 20-50% of the Alzheimer’s disease (AD) patients and depressive symptoms may seriously increase care giver burden and are frequently the reason for hospitalization. The recognition of depression in AD is of practical clinical relevance since depressive symptoms in AD patients can be successfully treated with selective serotonin re-uptake inhibitors (SSRIs), whereas no effective treatment is, at present, available for AD itself.

HPA-axis hyperactivity is well established in both AD patients (Swaab et al., 1994) and patients with major depressive disorder (MDD) (Gerner et al., 1985) resulting in, e.g., increased plasma and cerebrospinal fluid (CSF) cortisol levels.
Based on these findings we hypothesized that HPA-axis activity in depressed AD patients is even higher than in non-depressed AD patients, resulting in higher CSF cortisol levels. In order to avoid a number of methodological pitfalls in this line of research we studied the CSF in depressed, transiently depressed and non-depressed AD patients and in controls, putting special emphasis on prospective longitudinal psychiatric evaluation at symptom level, clinical matching for severity of dementia and neuropathological matching for the severity of AD pathology, and neurological co-morbidity.

**Method**

Demented patients were studied at six-month intervals in the framework of a prospective longitudinal study of depression in AD in eight nursing homes, as described in detail before (Hoogendijk et al., 1999). Brain tissue was obtained from the Netherlands Brain Bank (coordinator Dr. R. Ravid). Written informed consent for brain autopsy and the use of the material and clinical information for research purposes was provided by the patient’s next of kin before subjects entered the study. The CSF of 25 patients fulfilling the NINCDS-ARDA and CERAD criteria for definite AD and 11 controls could be obtained. DSM-III-R criteria were used to diagnose a major depressive episode. At six-month intervals, the severity of the depression and dementia was determined by the Cornell scale and the Functional Assessment Staging (FAST), respectively. Post mortem, neuropathological evaluation took place with an estimation of the severity of AD changes according to the classification of Braak. All patients with major neuropathological co-morbidity were excluded. Six AD patients suffered from a major depressive episode according to DSM-III-R at death, with a minimum duration of three months and high scores on the Cornell scale (>10). They were matched for age and sex and severity of AD pathology with eight non-depressed AD patients, having low scores on the Cornell scale (<10) and 12 transiently depressed AD patients, who were not depressed in the last three months of life, but had suffered from a mood disorder during some part of their lives. Finally, AD patients were matched with 11 controls. In CSF cortisol was measured using a method previously described (Swaab et al., 1994). Differences among groups were statistically evaluated using Kruskal-Wallis and Mann-Whitney U test and the Spearman test was used for correlations. Statistical significance was set at p<0.05.

**Results**

AD patients (n=25) had higher mean CSF-cortisol levels (503 nmol/L ± Standard
Increased cerebrospinal fluid cortisol level in Alzheimer’s disease

deviation; SD=340) than controls (n=11, 234 nmol/L, SD=182, p=0.010). There was no difference in CSF-cortisol between depressed, non-depressed and transiently depressed AD patients (p=0.4) and CSF-cortisol levels were not correlated with the Cornell scores (r=-0.3, p=0.2).

Discussion
The finding of increased levels of CSF cortisol in AD confirms our earlier results (Swaab et al., 1994). The result that the CSF cortisol levels in depressed AD patients are not different, and certainly not higher, than that of non-depressed AD patients, however, is in contrast with the situation in MDD (Gerner et al., 1985). Since CSF cortisol levels have been shown to be related to the severity of dementia (Miller et al., 1998), it is crucial in this type of research that the AD patients in the depressed group are exactly as demented as the AD patients in the non-depressed group, since a slightly more severe AD pathology in the depressed AD group would go together with a supplementary rise in CSF cortisol in this group. Matching for co-variables of dementia severity is, however, complicated by a number of methodological pitfalls. Firstly, depression and dementia have a number of symptoms in common, e.g. loss of interest, decreased energy, difficulty in thinking or concentrating, and psychomotor agitation or retardation (Hoogendijk et al., 1999). In order to control for symptom overlap we used the Cornell scale, which was specifically developed for the assessment of depression in all stages of dementia. The second pitfall is that it may be difficult to clinically distinguish levels of severity of dementia in the final stages of AD (bottom effect) (Hoogendijk et al., 1999). Therefore, we determined FAST scores every six months and, importantly, quantified neuropathological AD changes. However, contrary to earlier findings that showed a correlation between clinical AD parameters and higher cortisol levels (Miller et al., 1998), in the present study we found no relation between CSF cortisol and the neuropathological parameters of AD. Our data, thus, do not support the hypothesis that the co-morbidity of depression in AD has a neuropathological substratum in the HPA-axis or might benefit from e.g. glucocorticoid receptor antagonists, that are presently in development as antidepressants.

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Reference List


