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Cognitive and Noncognitive Symptoms in Dementia Patients: Relationship to Cortisol and Dehydroepiandrosterone

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ABSTRACT. We investigated the relationship between basal cortisol and dehydroepiandrosterone (DHEA) levels and impairment in different cognitive and noncognitive measures and the possible interaction of DHEA with hypercortisolemia in dementia in 27 patients diagnosed with Alzheimer's disease (AD). There were 17 men and 10 women. Patients were mildly to moderately cognitively impaired at the time of the initial cortisol measures. Patients were administered the Alzheimer's Disease Assessment Scale (ADAS) and Folstein Mini-Mental State Examination (MMSE) at approximately 6-month intervals. Cortisol and DHEA were determined using conventional ^{125}I radioimmunoassay procedures. Pearson product-moment correlations among cortisol and DHEA measures and both initial and longitudinal clinical measures were calculated. There was a relationship between baseline 8 a.m. cortisol levels and cognitive function at the initial testing as measured by the ADAS cognitive measure, with higher cortisol levels being associated with a greater level of impairment. We did not document a relationship between cortisol or DHEA levels and noncognitive measures. There was a significant correlation between both the initial MMSE and ADAS cognitive measures and initial DHEA level, with lower DHEA levels unexpectedly being associated with better performance on these measures. The initial DHEA levels did not predict decline in cognitive function over time. These findings bring into question the potential usefulness of DHEA as a therapeutic agent.

The purpose of this report is to present initial findings of a longitudinal study attempting to define the relationship of cognitive and noncognitive symptoms to cortisol and dehydroepiandrosterone (DHEA) in dementia patients. Prior work has suggested a relationship between dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and cognitive impairment in both depressed and demented patients (Dodt et al., 1991; Leake et al., 1990; Lesch et al., 1990; Skare et al., 1990; Suemaru et al., 1991). The observation in animals that prolonged exposure to high plasma cortisol levels causes irreversible hippocampal damage (Gurevich et al., 1990) has led to speculations that increased levels of corticosteroids are neurotoxic (Swaab et al., 1994) and that long-term hypercortisolemia may accelerate the dementia process (Hoyer et al., 1996).

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Although a number of abnormalities have been reported in HPA axis activity in Alzheimer's disease (AD), e.g., decreased adrenocorticotropic hormone (ACTH) levels in cerebrospinal fluid (CSF) (Nappi et al., 1988; Suemaru et al., 1991), elevated urinary free cortisol (Maeda et al., 1991), elevated corticotropin-releasing factor (CRF) in CSF (Martignoni et al., 1990a, 1990b), elevated rates of non-suppression of cortisol in response to the dexamethasone suppression test (DST) (Bilikiewicz & Bidzan, 1990; Davous et al., 1988; Ferrier et al., 1988; Gieri et al., 1987; Gurevich et al., 1989, 1990; Hatzinger et al., 1995; Leake et al., 1990; Maeda et al., 1991; Masugi et al., 1989; Molchan et al., 1990; Oxenkrug et al., 1989; Parnetti et al., 1990; Serby et al., 1988; Siegel et al., 1989; Skare et al., 1990; Vollhardt et al., 1989), and elevated baseline cortisol levels (Masugi et al., 1989; O'Brien et al., 1996; Tollefson et al., 1989), others have failed to replicate these findings. Roelandts (1989) found no difference in ACTH estimations in the CSF of 17 patients with dementia. Suemaru and colleagues (1991) reported decreased CRF in the CSF of AD patients. Ferrier and co-workers (1988) found that depressed patients as well as AD patients showed a similar elevation of cortisol after dexamethasone (DEX) administration. Davous and colleagues (1988) reported that AD patients showed normal baseline cortisol values. Leake and co-workers (1990) measured cortisol and ACTH in AD patients; cortisol was elevated only after DEX, as was ACTH. Sample differences in age, stage of disease, and degree of comorbid depression may account for these disparities in findings among studies.

The question still remains as to the relationship between hypercortisolemia and dementia. Deshmukh (1990) proposed that failure to terminate the HPA axis response in response to stress in AD leads to chronic excessive secretion of neurohormones including cortisol, resulting in progressive cognitive-affective-behavioral disorganization that is typical of dementia of the Alzheimer type. An alternate explanation is that loss of feedback control reflects less specific central nervous system (CNS) changes in late AD. Seckl and colleagues (1993) found maintenance of hippocampal glucocorticoid gene expression in the presence of an increased feedback signal, suggesting loss of the cholinergic innervation.

There have been varying reports on the relationship between dementia severity and cortisol levels. Bilikiewicz and colleagues (1990) noted a positive correlation between basal cortisol level and the severity of dementia only in simple dementia, whereas Suemaru and coworkers (1993) reported that the severity of dementia did not affect a.m. plasma cortisol levels. Gurevich and colleagues (1990) reported a decrease in HPA axis responsivity significantly correlated with greater cognitive impairment. Although 8 of 12 studies (67%) in Skare's review (1990) did not find a significant relationship between DST results and dementia severity in dementia patients without depression, several did report such a relationship. Balldin and colleagues (1994) and Siegel and co-workers (1989) reported a positive correlation between level of impairment and post-DEX cortisol levels. Oxenkrug and colleagues (1989) reported a positive Spearman rank correlation between the Global Deterioration Scale (GDS) scores and post-DEX cortisol levels in female patients, but not in men. Gurevich and colleagues (1989) found that the more severely impaired

patients had significantly higher post-DEX cortisol levels but did not have significantly higher pre-DEX cortisol levels, indicating a less responsive HPA axis in those patients. Serby and co-workers (1988) found that the highest degree of nonsuppression was seen in patients with GDS scores of 5 and 6. An unexpected finding was that a large number of severely impaired patients with GDS scores of 7 demonstrated normal post-DEX suppression. Again, all of these studies were cross-sectional, i.e., performed at a single time point. Thus, it is difficult to conclude from these studies whether HPA axis activity plays a causal role in the rate of cognitive decline.

More recently, DHEA has been proposed as a "fountain of youth." DHEA levels decline steeply through old age (Hornsby, 1995), reaching levels at age 80 that are about 20% of those at age 20 (Vermeulen, 1995). A decreased concentration of dehydroepiandrosterone sulfate (DHEA-S) in patients with AD has been reported but is still controversial. Legrain and co-workers (1995) and Yanase and colleagues (1996) found that serum concentrations of DHEA among controls, patients with AD, and patients with cerebrovascular disease did not significantly differ from one another. The evidence that DHEA can inhibit corticosteroid actions (Murphy, 1991), given the hypercortisolemia associated with dementia, makes it interesting to investigate together with cortisol in the AD population longitudinally.

In summary, despite the wealth of data accumulated in these previous studies, there remain questions about the relationship of cognitive and noncognitive symptoms to cortisol and DHEA in dementia patients. These include the effects of hypercortisolemia and DHEA over time, and the possible interaction of DHEA with the hypercortisolemia in dementia. The purpose of this study is to address these questions.

METHOD

Subjects

All 27 patients in this report had a diagnosis of probable AD by criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984) at entry into a longitudinal study of AD at the Stanford-VA Aging Clinical Research Center. To determine the diagnosis of probable AD, all subjects had a complete medical, psychiatric, neurologic, neuroimaging, and neuropsychological assessment. On the basis of these evaluations, a consensus diagnosis was reached by an interdisciplinary team including one to three physicians. Written informed consent was obtained from patients or from their caregivers for clinical and cortisol studies.

At the time of cortisol/DHEA measurements, no subject had active major medical problems such as recent cancer, endocrine disorders, or recurrent infections. None had a current diagnosis of major depressive disorder or other DSM-III-R (*Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, revised; American Psychiatric Association, 1987) Axis I diagnosis of major psychiatric syndrome, and none of the subjects were taking antidepressants or antidementia medications. Women taking estrogen replacement therapy and stabilized at

the same dose for 6 months or longer were included.

The basic demographics of the sample are presented in Table 1. There were 17 men and 10 women. Patients were mildly to moderately cognitively impaired at the time of the cortisol study because most were recruited to participate in the cortisol study as they entered the longitudinal study, which requires at entry a score of 15 or higher on the Mini-Mental State Examination (MMSE; Folstein et al., 1975). We did not recruit into this study patients whose MMSE scores were below 5 because many would be too impaired for extensive longitudinal follow-up with the MMSE and many would be too restless to comply with the full cortisol study protocol.

Cognitive and Noncognitive Measures

In addition to the MMSE, patients received the Alzheimer's Disease Assessment Scale (ADAS) regularly at approximately 6-month intervals. Both cognitive and noncognitive ADAS measures were performed. Cognitive ADAS scores can range from 0 to 70 whereas noncognitive scores can range from 0 to 50, with higher scores in both cases reflecting more severe pathology. The noncognitive scores include items such as depression and other behavioral symptoms. The 6-month measure closest to the cortisol determination was used in cross-sectional analyses. The average number of days between cortisol determination and cognitive testing was 46.3 (57.9). Mean scores on these measures are also presented in Table 1.

In addition, where two or more MMSE or ADAS measures were available, difference scores were computed for these measures, and yearly rate of change on the measures was computed by dividing the difference scores by the number of days between the first and last measurement. Thus, a MMSE change score of -2 indicates a loss of 2 points per year on the MMSE whereas an ADAS cognitive (ADAS-Cog) change score of 7 indicates a gain of 7 points per year on the ADAS-Cog measure. Both such scores would indicate deterioration in the cognitive status of the patient. Mean values for these scores are presented in Table 2 along with the average duration of follow-up.

Cortisol and DHEA Measures

Patients had blood drawn for cortisol determinations at 8 a.m., 1 p.m., 1:30 p.m.,

TABLE 1. Basic Background Measures, Cognitive Measures, and Biological Measures at Baseline

Variable	No. of Subjects	Mean	*SD*	Minimum	Maximum
Age, years	27	71.7	8.0	51.3	84.5
MMSE total score	27	19.1	5.5	8.0	28.0
ADAS-Cognitive score	27	19.5	9.3	8.7	42.0
ADAS-Noncognitive score	27	4.9	2.8	0	11.0
8 a.m. Cortisol, μg/ml	26	268.4	75.0	174.6	441.4
p.m. Cortisol, μg/ml	27	142.6	47.7	75.7	239.9
DHEA, μg/ml	25	0.53	0.38	0.13	1.77

Note. MMSE = Mini-Mental State Examination; ADAS = Alzheimer's Disease Assessment Scale; DHEA = dehydroepiandrosterone.

TABLE 2. Age, Cognitive Change Measures, and Biological Measures for Subjects With Longitudinal Follow-Up

Variable	No. of Subjects	Mean	*SD*
Age, years	16	71.4	8.8
MMSE score change	16	–2.1	3.8
ADAS-Cognitive score change	16	7.4	7.8
ADAS-Noncognitive score change	16	0.7	2.6
8 a.m. Cortisol, μg/ml	15	246.3	73.1
p.m. Cortisol, μg/ml	16	139.5	51.1
DHEA, μg/ml	16	0.5	0.3
Duration of follow-up, years	16	1.7	0.4

Note. Abbreviations as in Table 1.

2 p.m., 2:30 p.m., 3 p.m., 3:30 p.m., and 4 p.m. Values reported in the following analyses include the 8 a.m. value and the mean of the six afternoon values, to be called the p.m. value. One 8:00 a.m. cortisol level could not be determined due to technical reasons.

In addition, DHEA levels were determined from the 8 a.m. and 4 p.m. samples. An average of these two measures was used. Two DHEA levels could not be determined due to technical reasons. Cortisol and DHEA were determined using conventional ^{125}I radioimmunoassay procedures. Mean values for cortisol levels and DHEA levels are presented in Table 1.

RESULTS

Correlations Among Cortisol and DHEA Measures and Age

To obtain basic information about the interrelations among biochemical variables and their relation to age in this sample of patients, product-moment correlations were computed among cortisol and DHEA measures and age. The mean DHEA level for men was 0.57 μg/ml (0.42) and the mean DHEA level for women was 0.44 μg/ml (0.28). Mean values for all cortisol levels and DHEA levels are presented in Table 1 and the correlations are presented in Table 3.

Correlations Among Cortisol and DHEA Measures and Initial Clinical Measures

Pearson product-moment correlations among cortisol and DHEA measures and initial clinical measures were calculated and are presented in Table 4. The relationship between DHEA measures and MMSE and ADAS-Cog is presented in Figures 1 and 2.

Correlations Among Cortisol and DHEA Measures and Longitudinal Clinical Measures

Pearson product-moment correlations among cortisol and DHEA measures and longitudinal clinical measures were calculated and are presented in Table 5.

DISCUSSION

The results of this study should be considered preliminary and hypothesis-generating rather than hypothesis-testing. Nonetheless, there are some interesting findings in the results. First of all, there

appears to be a relationship between baseline 8 a.m. cortisol levels and cognitive function at the initial testing as measured by the ADAS-Cog, with higher cortisol levels being associated with a greater level of impairment. This relationship cannot be documented on the p.m. measure of cortisol despite the observation that the a.m. and p.m. scores are strongly correlated ($r = .52$). This finding is surprising given prior work that has indicated that the p.m. cortisol measure is reflective of the mean 24-hour cortisol value (Halbreich et al., 1985). Nonetheless, the finding is consistent with other work that documents a relationship between cortisol levels and cognitive impairment (Lupien et al., 1994). Furthermore, our limited longitudinal data suggest that the a.m. data may be related to decline in

TABLE 3. Correlations Among Cortisol and DHEA Measures and Age

	8 a.m. Cortisol	p.m. Cortisol	DHEA	Age
8 a.m. Cortisol		.51774	.02	−.19
Unadjusted *p* value		.0067	.91	.35
n		26	24	26
p.m. Cortisol			−.32	.09
Unadjusted *p* value			.1237	.66
n			25	27
DHEA				−.39
Unadjusted *p* value				.06
n				25

Note. Values are Pearson product-moment correlations. DHEA = dehydroepiandrosterone.

TABLE 4. Correlations Among Cortisol and DHEA Measures and Initial Clinical Measures

	8 a.m. Cortisol	p.m. Cortisol	DHEA	Age
MMSE	−.21	.04	−.62 (−.63)	.02
Unadjusted *p* value	.30	.86	.001	.91
n	26	27	25	27
ADAS-Cognitive	.54	.04	.45 (.47)	−.22
Unadjusted *p* value	.01	.84	.02	.26
n	26	27	25	27
ADAS-Noncognitive	.25	−.01	.31	.02
Unadjusted *p* value	.22	.95	.13	.93
n	26	27	25	27

Note. Values are Pearson product-moment correlations (Spearman rank correlations in parentheses). Abbreviations as in Table 1.

cognitive function longitudinally. More data over a longer period than the mean of 1.7 years of this study will be needed to resolve this issue fully.

The DHEA levels obtained in this study are consistent with those found in other studies with trends to higher levels in men than in women and with a trend toward an inverse relationship with age. We also found no correlation between DHEA and cortisol levels, consistent with the report of Legrain and colleagues (1995). Of interest is the finding that there was a significant correlation between both the initial MMSE and the ADAS-Cog measures and initial DHEA level, with lower DHEA levels unexpectedly being associated with better performance on these measures. This

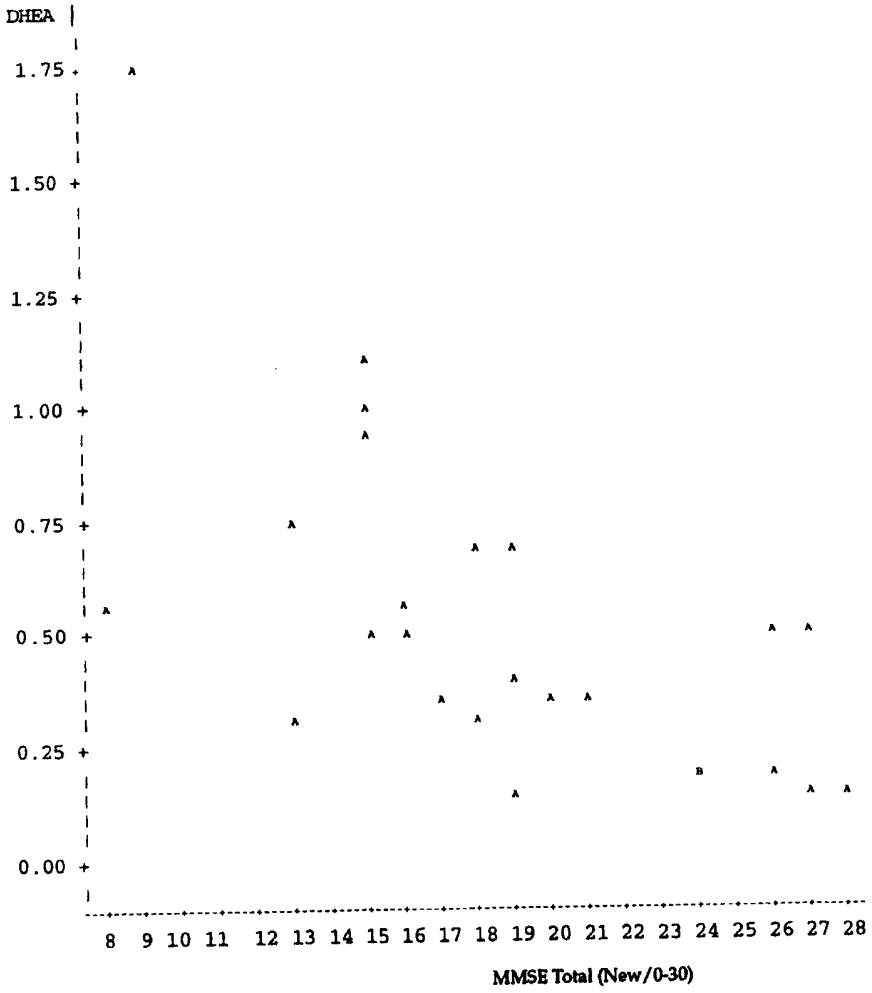

Figure 1. Plot of DHEA and MMSE total score. A = 1 observation; B = 2 observations; DHEA = dehydroepiandrosterone; MMSE = Mini-Mental State Examination.

is in contrast to Wolkowitz and colleagues' (1995) report of administration of DHEA leading to improvement in automatic memory function. The initial DHEA levels, however, show no relationship predicting decline in cognitive function over time. These findings bring into question the potential effectiveness of DHEA as a therapeutic agent in AD. However, clinical, double-blind trials are still needed to answer this question.

Finally, we did not document a relationship between cortisol or DHEA levels and noncognitive measures. This is unanticipated given the established literature relating cortisol levels to depressive symptoms (Rothschild et al., 1989) and DHEA administration to improvement

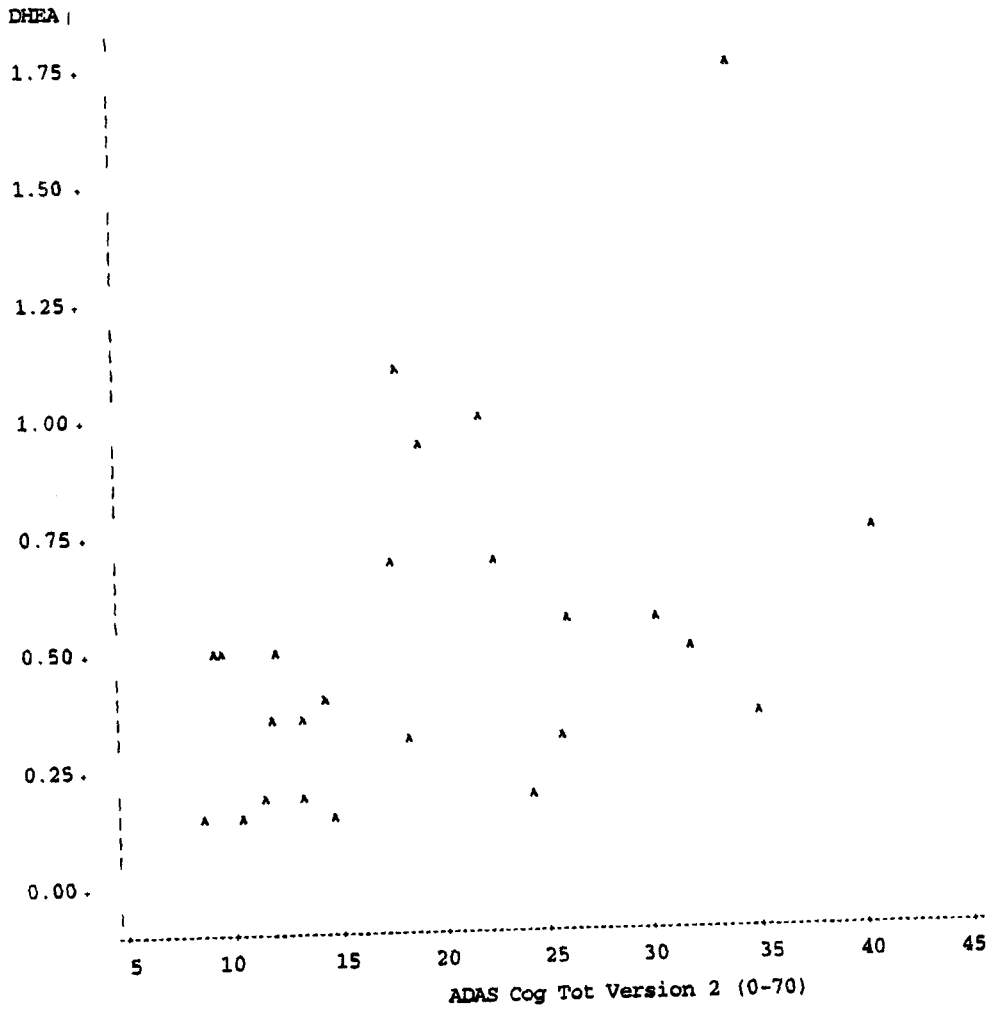

Figure 2. Plot of DHEA and ADAS-Cog. *Note:* 2 observations had missing values. DHEA = dehydroepiandrosterone; ADAS-Cog = cognitive measure of the Alzheimer's Disease Assessment Scale.

TABLE 5. Correlations Among Cortisol and DHEA Measures and Longitudinal Clinical Measures

	8 a.m. Cortisol	p.m. Cortisol	DHEA	Age
MMSE Change	−.17	−.07	.10	.00
Unadjusted *p* value	.53	.78	.71	.99
n	15	16	16	16
ADAS-Cognitive change	.49	.26	.15	−.24
Unadjusted *p* value	.07	.33	.57	.37
n	15	16	16	16
ADAS-Noncognitive change	−.04	.01	.14	−.16
Unadjusted *p* value	.89	.96	.60	.55
n	15	16	16	16

Note. Values are Pearson product-moment correlations. Abbreviations as in Table 1.

in depression (Wolkowitz, 1995). Our lack of findings may be due in part to the very low levels of behavioral disturbance seen in these patients. The mean ADAS noncognitive score was only 5 on a 50-point scale. Thus there was little behavioral pathology to correlate with any biological measure. This itself is likely due to the relatively early stage of disease of these patients with a mean MMSE score of 19 at the initial testing. Our plan is to continue to follow these patients and obtain behavioral ratings over time as more symptoms are likely to develop as well as to measure cortisol levels and DHEA levels on a yearly basis to determine the relationship of these biological markers to the development of behavioral symptoms over time.

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