Elevated Urinary Free Cortisol in Patients With Dementia

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MAEDA, K., K. TANIMOTO, T. TERADA, T. SHINTANI AND T. KAKIGI. Elevated urinary free cortisol in patients with dementia. NEUROBIOLOG AGING 12(2) 161-163, 1991.—Urinary free cortisol (UFC), 17-hydroxycorticosteroids (17-OHCS) in urine and dexamethasone suppression test (DST) were examined in patients with dementia of Alzheimer type (DAT) and multi-infarct dementia (MID), and nondemented elderly. Eight of 19 patients (42.1%) were DST nonsuppressor. UFC was significantly elevated in patients with dementia, compared with that in nondemented elderly. There was no difference in UFC levels between DAT and MID. The UFC level correlated with post-DST plasma cortisol level at 1600 in demented patients. The mean level of 17-OHCS in demented patients was increased, although the difference was not significant statistically. In demented patients, UFC levels, not 17-OHCS levels in urine were correlated with Mini-Mental State Examination scores. These results suggest that a hypothalamo-pituitary-adrenal axis function is activated in demented patients and that this activation relates generally to dementation itself, not to an etiology of dementia. Measurement of UFC might be a biological marker of dementia and may have a value in diagnosis of dementia.

Urinary free cortisol 17-OHCS Dexamethasone suppression test Dementia of Alzheimer type
Multi-infarct dementia

A hyperactive hypothalamo-pituitary adrenal (HPA) axis function in depression has been demonstrated by many investigators (2). An abnormal dexamethasone test (DST) result, a blunted circadian variation of plasma cortisol, an elevated nocturnal cortisol secretion, an increased cerebrospinal fluid (CSF) cortisol level and a high urinary free cortisol (UFC) level have been described in depression (19).

On the other hand, it is well established that diagnostic differentiation of depression from dementia can be complicated. Depression frequently occurs in demented patients. Depression exhibiting dementia-like symptoms is known as pseudodementia. Recently, several investigators have found a high incidence of abnormal DST results and a disturbed circadian variation of plasma cortisol (5, 8, 16, 18) in a group of patients with dementia. Non-suppression in DST, however, was not completely synonymous with cortisol hypersecretion. A twenty-four-hour urinary steroids determination has been considered to provide a more accurate estimation of overall cortisol secretion (12).

The present study was designed to determine if 1) UFC and 17-OHCS levels in urine are elevated in demented patients, as in depressed patients, 2) there is a difference between dementia of the Alzheimer type (DAT) and multi-infarct dementia (MID) in steroids excretion.

METHOD

The study consisted of 19 inpatients who met the criteria of DSM-III-R (6) and 12 nondemented elderly (Table 1). The diagnosis for dementia was made by medical and psychiatric history, physical examination, CT scan, magnetic resonance imaging, and CSF and blood analysis. The differentiation between DAT (primary degenerative dementia of the Alzheimer type in DSM-III-R) and MID was made according to the criteria of DSM-III-R. To confirm the presence of global intellectual deterioration, we also examined the patient’s scores on the Mini-Mental State Examination (MMSE) (7). All patients and subjects were free of severe medical illness and medication reported to affect cortisol secretion (3). None of them met DSM-III-R criteria for major depression. Depression symptoms were also rated on the Hamilton rating scale for depression (9) in these subjects and no patient showed scores higher than seven.

Urine excreted for 24 hours was collected. All urine samples excreted for 24 hours from demented patients were collected

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Through a balloon catheter, UFC was extracted into ten times volume of methylene chloride (14). Urinary 17-OHCS was determined by the modification of Porter and Silber's method (15) (Wako Co., Osaka). One mg of dexamethasone was administered orally at 2200 and blood samples were taken at 0800 and 1600 on the following day. Nonsuppression in DST was defined that a plasma cortisol level of at least one of two blood samples was over 5 μg/dl. Urinary and plasma cortisol was measured with solid phase radioimmunoassay (17) (Daichi Radioisotope, Tokyo). The recovery of UFC assay was 92%. Statistical analysis was performed with Student's t-test (demented vs. control), and relationships between two variables were examined with Wilcoxon signed-rank test.

**RESULTS**

A nonsuppression in DST was observed in none of the control subjects and eight, 42.1% of the demented patients (Table 1), which is consistent with previous reports (8, 16, 18). The MMSE score of patients with dementia and nondemented elderly were 11.6 ± 3.6 (mean ± SEM) and 28.8 ± 0.6, respectively. The UFC concentration in the 12 elderly controls, 97.1 ± 13.8 μg/day was similar to that reported previously by other investigators (14, 17). The UFC concentration in 19 patients with dementia, 256.3 ± 28.8 μg/day, was significantly (p<0.01) greater than that in 12 nondemented elderly (Fig. 1). There was no difference in UFC levels between DAT and MID. UFC levels correlated with post-DST plasma cortisol levels at 1600 in demented patients (p<0.05). Although a 24-hour urinary excretion of 17-OHCS in demented patients was higher than that in nondemented subjects, the difference was not statistically significant. There was a highly significant correlation (p<0.01) between UFC levels and 17-OHCS excretion in all subjects. MMSE scores of demented patients correlated with UFC levels (p<0.05), not with 17-OHCS concentrations.

**DISCUSSION**

Multiple cerebrovascular accidents in patients with MID were usually confirmed by CT scan and MRI. The patients with DAT in this study met the criteria of DSM-III-R for primary degenerative dementia of the Alzheimer type and not for major depression. These patients did not exhibit depressive symptoms. Therefore, it is unlikely that the elevated UFC excretion in de-
mentia is due to depressive symptoms.

We also found an elevation in urinary 17-OHCS in demented patients, although the difference was not statistically significant. A similar result has been reported in depression by Carroll et al. (2) that 24-hour UFC concentration, not 17-OHCS, is significantly increased and they concluded that UFC excretion is more sensitive than 17-OHCS in urine in distinguishing depression from other neuropsychiatric disorders.

UFC is considered to reflect plasma free cortisol level which is the most active substance in circulation and proved to be more valuable for the detection of hyperfunction of the adrenal cortex (4). An abnormal DST result, a disturbed circadian variation of plasma cortisol and a nocturnal cortisol hypersecretion have been reported in patients with dementia (5,8). A UFC level in demented patients has not been demonstrated before. This indicates that there exists overall hyperfunction in HPA axis in patients with dementia.

The cortisol secretion is regulated by a number of neurotransmitters, specifically norepinephrine and acetylccholine. A hyperactive HPA axis function in depression has been considered due to a diminished noradrenergic tone in the limbic system (2), because noradrenergic input inhibits HPA axis function in rats (10). In the brain from senile dementia, the concentration of noradrenaline in the hypothalamus was one-third of that of healthy aged subjects and cell loss in the locus coeruleus which contains the cell bodies of noradrenergic neurons which project to the hypothalamus has been demonstrated (1). Davies et al. (5) have demonstrated that 3-methoxy-4-hydroxyphenyl-glycol (MHPG), a noradrenaline metabolite, in CSF, negatively correlated with mean nocturnal cortisol in both patients with Alzheimer’s disease and nondemented aged control subjects. A low noradrenaline level in the hypothalamus in demented patients could be explained an elevated excretion of UFC.

The loss of acetylcholine-containing cells exists in the hypothalamus in Alzheimer’s disease (13). Decreased cholinergic input, however, results in diminishing cortisol secretion (11). The deficit in cholinergic systems do not explain the hypersecretion of cortisol.

These results indicate that an abnormal HPA axis function, which is not related age or a depressive state, exists in demented patients. An abnormal HPA axis function, specifically UFC measurement, might be useful as a biological marker of dementia.

REFERENCES