Abnormalities at Different Levels of the Hypothalamic-Pituitary-Adrenocortical Axis Early After Stroke

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Background and Purpose: Hypercortisolism is common in stroke patients. The aim of this study was to investigate possible disturbances at different sites within the hypothalamic-pituitary-adrenal axis. We also studied possible associations between hypercortisolism and clinical manifestations of brain dysfunction.

Methods: Patients with an acute ischemic stroke (n=16; mean±SD age, 71±11 years) were compared with healthy elderly subjects (n=9). We performed a short adrenocorticotropic hormone (ACTH) test with 0.25 mg 1-24 ACTH injected intravenously and an overnight dexamethasone suppression test with 1 mg dexamethasone given orally at 11 PM.

Results: Serum cortisol levels after dexamethasone at 8 AM were significantly higher in stroke patients (p=0.003). The area under the curve for the cortisol response to ACTH was elevated in seven (47%) of stroke patients, and the centered cumulative cortisol response was elevated in three (20%) patients. The area under the curve response correlated significantly to the presence of an acute confusional state and male sex in stroke patients (r=0.63 and r=0.62, respectively; p<0.05), whereas the centered cumulative cortisol response diminished with increasing age (r=−0.62; p<0.05). Postdexamethasone cortisol levels were significantly correlated to the presence of an acute confusional state and to extensive limb paresis (r=0.66 and r=0.62, respectively; p<0.05).

Conclusions: There are abnormalities in the cortisol axis both at the central level and at the adrenal level early after stroke. Hypercortisolism is closely associated with cognitive disturbances and extensive motor impairment. (Stroke 1992;23:1573-1576)

KEY WORDS • cerebral ischemia • cerebrovascular disorders • cortisol

Many patients with acute stroke show a pronounced hypercortisolism. Increased plasma and urinary cortisol levels are associated with greater mortality and a poorer functional outcome after stroke. This association has also been demonstrated in other types of brain injury. Theoretically, dysregulation at several sites within the hypothalamic-pituitary-adrenocortical axis may contribute. This includes an increased production rate of cortisol, a change in metabolism and/or clearance rate of cortisol, an increased sensitivity to stimulation of the adrenal glands, and a decreased "shut-off" mechanism of the cortisol axis.

In patients with chronic degenerative cerebral disease such as Alzheimer's disease a correlation between cognitive disturbances and hypercortisolism has been demonstrated. It has been hypothesized that hypercortisolism per se may contribute to cognitive disturbances. The acute confusional state commonly occurs in elderly hospitalized patients and may be particularly frequent among stroke patients.

It is therefore of interest to study in more detail the different sites within the cortisol axis where possible abnormalities can lead to hypercortisolism early after stroke. Furthermore, we wanted to examine whether there was an association between cortisol levels and acute confusional state and/or motor impairment in these patients.

Subjects and Methods

Sixteen patients (11 men, five women; mean±SD age, 71±11 years) with an acute brain infarction were selected for this study from our stroke unit. The median delay from onset until admission was 11 hours (range, 1-100 hours). Based on clinical judgement and on the results of computed tomographic (CT) scans, performed in all patients, 14 patients had a supratentorial brain infarction and two patients had a cerebellar infarction. In the supratentorial brain infarction group, eight patients had a probable nonembolic brain infarction, five patients had an embolic brain infarction, and one patient had a lacunar infarction. Six of the patients in this group had right-sided and eight had left-sided brain lesions. These patients all had an extremity paresis afflicting the contralateral arm or leg at admission. Three patients with left-sided brain lesions also had a...
slight-to-moderate dysphasia at admission. Both patients with cerebellar infarctions had vertigo, one of them having a right-sided arm paresis as well. None of the patients had a pronounced decrease in consciousness, i.e., more than drowsiness, high fever (>38.5°C), renal failure (plasma creatinine level >200 μmol/l), known extensive weight loss or malnutrition, hypothyroidism/hyperthyroidism, pituitary insufficiency, uncontrolled diabetes mellitus, obvious abstinence reactions from alcohol or other central nervous stimulants, or epilepsy. None was treated with medications known to interfere with the test results such as glucocorticoids, estrogens, anticonvulsants, high-dose benzodiazepines, or ephedrine. Two of the patients had non-insulin-dependent diabetes mellitus.

As control subjects, nine healthy elderly people were selected from an ongoing study of hormone changes in the elderly (six men, three women; mean±SD age, 71±9 years). All were thoroughly investigated by a resident in geriatric medicine. CT scan of the brain was normal in all individuals, and none were taking drugs.

The patients were examined between the third and seventh day after admission. They were investigated in a standardized manner, with repeated clinical assessments. The extent of extremity paresis (i.e., of the extremity mostly afflicted) was quantified using a four-point scale.3 Acute confusional state was diagnosed using criteria from the Diagnostic and Statistical Manual of Mental Disorders, edition 3, revised (DSM-III-R).11,12 A diagnosis of a major depressive episode was based on criteria from DSM-III-R.12 All tests and interviews with patients, relatives, and staff regarding the diagnoses of acute confusional state and major depression were made by one of the authors.

A short adrenocorticotropic hormone (ACTH) stimulation test was performed in the fasting state between 8 and 9 AM. In this test 0.25 mg ACTH (1-24 ACTH, Synacthen, CIBA-Geigy) was administered slowly intravenously as a bolus dose. Blood was collected for cortisol analyses before the injection and 30 and 60 minutes after the injection. This was followed by an overnight dexamethasone suppression test in which 1 mg dexamethasone (Decadron, Merck Sharp & Dohme International) was given orally at 11 PM. Blood was drawn on the following day at 8 AM for serum cortisol analysis. Serum cortisol was analyzed with a radioimmunoassay kit (Farmos Diagnostica, Turku, Finland) with an interassay coefficient variation <8% for the analysis. The area under the curve for the cortisol response to ACTH was calculated by the trapezium rule.13 The centered cumulative cortisol response to ACTH was calculated using the following formula: area under the curve−(basal serum cortisol level×60).13

The data were analyzed using the computerized statistical program SYSTAT.14 Differences in cortisol levels between groups were analyzed with the Mann-Whitney U test. Spearman correlation coefficients (r_s) were used for the calculation of correlations.

Results

Basal serum cortisol levels were nonsignificantly higher in stroke patients compared with control subjects (mean±SD serum cortisol levels, 387±195 versus 361±82 nmol/l). Serum cortisol levels were significantly higher in stroke patients after dexamethasone (Figure 1; 179±170 versus 31±7 nmol/l; p=0.003). Six of the patients (38%) were nonsuppressors to dexamethasone by conventional criteria; i.e., they had a serum cortisol level >138 nmol/l after dexamethasone.15 The healthy control subjects were all suppressors to dexamethasone; the highest postdexamethasone cortisol level in the control group was 47 nmol/l.

Stroke patients had a higher responsiveness to ACTH, although not significantly so (serum cortisol after 30 minutes, 802±226 versus 688±115 nmol/l, p=0.23). The area under the curve for the cortisol response after ACTH was clearly elevated in seven (47%) of the stroke patients (Figure 2) compared with the control group. The centered cumulative response was elevated above the upper limit for control subjects in three (20%) of the patients. When the highest

![Figure 1. Scatterplot of serum cortisol levels at 8 AM after dexamethasone. Controls, healthy elderly subjects (n=9); Stroke, stroke patients (n=15). One patient was excluded because of lack of data. Mann-Whitney U test was used for statistical analysis.](image1)

![Figure 2. Scatterplot of serum cortisol response to adrenocorticotropic hormone expressed as area under the curve response. Area under the curve was calculated by the trapezium rule. Controls, healthy elderly subjects (n=9); Stroke, stroke patients (n=15). One patient was excluded because of lack of data.](image2)
postdexamethasone serum cortisol level (47 nmol) in the healthy elderly group was used as an arbitrary cutoff point with the highest area under the curve response to ACTH in the control group (43,020 nmol/l/min) as the other cutoff point there was a significant association between nonsuppressibility to dexamethasone and excessive area under the curve response to ACTH (p=0.005; Fisher’s exact test). This association did not remain significant when the centered cumulative cortisol response was used instead of the area under the curve response (p=0.22). The stroke patients with a “normal response” to ACTH, i.e., an area under the curve response <43,020 nmol/l/min, were still more responsive to dexamethasone compared with control subjects (p=0.003).

None of the patients were judged to have a major depression. However, five of the 16 patients were diagnosed as having an acute confusional state when the tests were made. Patients with acute confusional state had a significantly increased cortisol response 30 minutes after ACTH compared with patients without confusion (Figure 3). The cortisol response after 60 minutes was slightly higher in patients with acute confusional state. However, there was only a tendency toward a higher area under the curve and centered cumulative cortisol response in this group of patients (55,196±7,711 versus 39,171±9,352 and 28,241±11,648 versus 19,142±7,509 nmol/l/min; p=0.16 and p=0.46, respectively). Seven patients (44%) had some degree of limb paresis.

The response to ACTH after 30 minutes in stroke patients was significantly correlated to male sex, extensive limb paresis, and acute confusional state (r_s=0.63, 0.63, and 0.55, respectively; p<0.05). Furthermore, limb paresis and acute confusional state were strongly positively correlated (r_s=0.86; p<0.001). The area under the curve response for cortisol to ACTH was significantly associated with acute confusional state and male sex in stroke patients (r_s=0.63 and r_s=0.62, respectively; p<0.05), whereas a moderate correlation to limb paresis was seen (r_s=0.45; NS). The centered cumulative cortisol response diminished with increasing age (r_s=0.62; p<0.05), whereas only a moderate correlation with acute confusion was seen (r_s=0.42; NS).

FIGURE 3. Line graph of serum cortisol before and after the administration of 0.25 mg i.v. adrenocorticotropic hormone (I-24 ACTH) to stroke patients (n=16). ACS, stroke patients with an acute confusional state according to DSM-III-R; Non-ACS, stroke patients without ACS. Mann-Whitney U test was used for statistical analysis.

Serum cortisol levels after dexamethasone in stroke patients were significantly correlated to the presence of acute confusional state and to limb paresis (r_s=0.66 and 0.62, respectively; p<0.05). Four of five patients with acute confusional state had a profoundly decreased suppression after dexamethasone, i.e., a serum cortisol level >200 nmol/l after dexamethasone, whereas none of the nonconfused patients had a postdexamethasone cortisol level above this value.

**Discussion**

This study indicates abnormalities in the hypothalamic-pituitary-adrenal axis both at a central level, i.e., a decreased suppressibility, and in the feed-forward, stimulatory arm of the cortisol axis early after stroke. An increased cortisol production rate has been shown in stroke patients, using both urinary free cortisol levels and isotope dilution methods. Based on our findings, an increased cortisol production rate early after stroke can, in some patients, be caused by an increased adrenal responsiveness to ACTH.

Repeated stresses are common for stroke patients, such as various cardiovascular complications, infections, and emotional reactions. These repeated stresses may increase the adrenal sensitivity to ACTH and therefore prolong the hypercortisolism. Furthermore, in a study of patients undergoing major abdominal surgery it was shown that the high levels of cortisol in the first 2 days after surgery were associated with increased levels of ACTH and corticotropin-releasing hormone, indicating an increased central drive. Thereafter the levels of ACTH and corticotropin-releasing hormone were suppressed to subnormal values, but the adrenal responsiveness to ACTH was increased. Thus, an increased adrenal responsiveness to ACTH may contribute to maintaining high circulating cortisol levels after stroke in some patients. Stimulating effects of cytokines on the cortisol axis and direct effects of a rise in intracranial pressure may also influence cortisol levels. These changes may be aggravated in the elderly, in whom the threshold for cortisol suppression seems to be elevated in various diseases such as major depression and after femoral neck fractures.

There seems to be a subgroup of patients who have a disturbance of the hypothalamic-pituitary-adrenocortical axis both centrally and peripherally. In our study cortisol axis abnormalities were confined mostly to patients with cognitive disturbances, preferably those with an extensive functional impairment. This is in line with earlier studies from our unit. Cognitive disturbances late after stroke have also been associated with high postdexamethasone cortisol levels. Furthermore, the occurrence of postoperative delirium was in one
study associated with a significant increase in circulating levels of cortisol. There also seems to be an association between hypercortisolism and major depression late after stroke, but this is not seen early after stroke.

Glucocorticoid receptors are present in the human brain, and high glucocorticoid levels, endogenous and/or exogenous, have been suggested to be toxic to neurons, especially in the hippocampus. In addition, the hippocampus seems to be very sensitive to ischemic brain damage, with experimental lesions causing impairments of learning and memory in rats. Theoretically, hypercortisolism could reinforce the ischemic damage to hippocampal neurons and thereby contribute to cognitive disturbances after stroke. Hippocampal activity normally inhibits the cortisol axis, as demonstrated by electrical stimulation in humans. Damage to hippocampal neurons can therefore be followed by hypercortisolism. This may be due to either a lesion-induced loss of a feedback site in the hippocampal system or an enhanced stimulation causing basal hypersecretion. In stroke patients these abnormalities may coexist.

In summary, we have shown both an increased responsiveness of the adrenal glands to ACTH and a decreased suppressibility to dexamethasone in subgroups of patients early after acute stroke. This indicates disturbances at several sites within the hypothalamic-pituitary-adrenocortical axis early after stroke. These changes seem to be associated mainly with cognitive disturbances in patients with pronounced neurologic deficits.

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