Hypercortisolism Revealed by the Dexamethasone Suppression Test With Acute Ischemic Stroke

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Using the dexamethasone suppression test, we studied the activity of the hypothalamic-pituitary-adrenal axis within the first week after onset in 62 patients with acute ischemic stroke. Compared with two control groups (one comprising 25 elderly patients with various acute medical disorders and the other comprising 33 80-year-old volunteers), stroke patients had higher postdexamethasone cortisol levels (p=0.08 and p=0.001, respectively). By multiple regression analysis, high postdexamethasone cortisol levels in the stroke patients were significantly associated with proximity of the lesion to the frontal pole of the brain (p=0.008) and with disorientation (p=0.03), whereas no association with major depression was seen. Many stroke patients are exposed to hypercortisolism, which may have negative consequences upon organ functions. The extent to which dexamethasone administration suppresses cortisol levels seems to be determined mainly by the site of brain lesion and cannot be used as an indicator of major depression early after stroke. (Stroke 1989;20:1685–1690)

Increased activity of the hypothalamic-pituitary-adrenal (HPA) axis, as well as of the sympathoadrenal system, is commonly seen in various forms of acute stress, including stroke.1–2 Hypercortisolism per se has potentially serious side effects on many organ systems,1 and a higher mortality rate has been described in stroke patients with a higher stress response, as measured by plasma cortisol levels and catecholamine excretion.2

Cognitive disturbances are common in acute stroke patients. In patients with chronic cognitive disturbances such as Alzheimer’s disease, a decreased ability of dexamethasone to suppress cortisol levels is a common finding.3 Depressive disorders and other emotional reactions are also frequently seen both early and during the rehabilitation phase after stroke.4,5 Major depression has been associated with heightened activity of the HPA axis, as measured by the dexamethasone suppression test.6–7 The use of this test has been suggested as a way to identify subtypes of depression in nonstroke8 as well as stroke9 patients. In the aftermath of stroke, high activity of the HPA axis has been associated with depression.9–12 Patients included in these earlier studies had had ischemic as well as hemorrhagic lesions at various locations and were studied at various times after the acute event.

The aim of our study was to investigate, using the dexamethasone suppression test in a well-defined sample of patients with ischemic supratentorial stroke during the acute phase, the function of the HPA axis, its relation to the brain lesion, and its association with major depression, physical impairments, and cognitive status.

Subjects and Methods

We selected patients from those admitted to our stroke unit. This unit has been described in detail13; it takes care of acute stroke patients who have had a stroke within 1 week before admission. From this prospectively studied cohort, we selected 62 patients (37 men and 25 women, mean±SD age 74.6±9.4 years) during 14 months. We included patients with an acute supratentorial ischemic stroke as judged by clinical examination and computed tomography (CT scan). Exclusion criteria were 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 and/or malnutrition, hypothyroidism or hyperthyroidism, pituitary insufficiency, uncontrolled diabetes mellitus, obvious abstinence reac-

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tions from alcohol and/or other central nervous system (CNS) stimulants, epilepsy, and certain medications (glucocorticoids, estrogens, anticonvulsants, high-dose benzodiazipines, ephedrine). Twelve patients had known and well-controlled diabetes mellitus.

The first control group consisted of 25 patients (13 men and 12 women, mean±SD age 76.8±8.4 years) admitted to the hospital because of various acute medical disorders. None of the control patients had known CNS disease, including previous stroke or epilepsy. The same exclusion criteria as for the stroke patients were applied regarding renal function, medications, etc. The second control group was selected from the official population census register of Umeå. Thirty-three randomly selected 80-year-old people were included; 20 were men and 13 were women. The same exclusion criteria (except for hospitalization) as for the first control group were used.

Informed consent was obtained from all subjects and/or their relatives, and the study was approved by the Ethics Committee of Umeå University.

The stroke patients were investigated between Days 3 and 7 after admission. Blood was drawn from all subjects at 7 AM after an overnight fast for the analysis of plasma cortisol. The subjects were given 1 mg dexamethasone orally (Merck Sharp & Dohme International, Rahway, New Jersey) at 11 PM the same day. Blood was drawn on the following day at 7 AM, 4 PM, and 11 PM for postdexamethasone plasma cortisol analyses. Cortisol was analyzed with a radioimmunoassay kit (Farmos Diagnostica, Turku, Finland). The interassay coefficient of variation for the analysis was 7.6%. Subjects with a postdexamethasone cortisol level of >138 nmol/1 at 7 AM, 4 PM, and/or 11 PM were considered to be nonsuppressors to dexamethasone.6

CT scans of the 62 stroke patients were analyzed by the same neuroradiologist, who was blinded to the clinical assessments. The following structural brain measurements were made: 1) brain volume, the sum of the volume of brain substance on three consecutive slices beginning with the first slice passing through the lateral ventricles; 2) relative lesion volume, the computer-calculated sum of the lesion volumes in each slice in which the lesion was visible divided by the overall brain volume; and 3) relative distance of the lesion from the frontal pole, the distance of the anterior border of the lesion from the frontal pole divided by the overall anteroposterior length of the cerebral hemisphere in the same slice. The lesions were classified as cortical and/or deep. Cortical lesions were further classified with regard to the lobes involved.14 The amount of edema surrounding the lesion was quantified using a four-point scale. The anterior horn index was defined as the maximum distance between the tips of the anterior horns divided by the maximum transverse inner diameter of the skull.13 Cortical brain atrophy was estimated using a three-point scale according to principles previously used at our radiology department.16 The presence of old lesions on CT scans was scored as yes or no for each patient.

All stroke patients were investigated in a standardized manner, with repeated clinical assessments. The extent of paresis (i.e., of the extremity most afflicted) on Day 4 after admission was quantified using a four-point scale. In a subsample of stroke patients, the paresis score correlated well with the activities of daily living scores of Katz et al17 (r=0.70, p<0.001). A three-point scale for orientation was used; the agreement between orientation score from two independent observers was 91%.

Stroke patients were interviewed 4–5 and 10 days after admission by the same psychiatrist who did not know the response to dexamethasone. Psychiatric diagnosis of a major depressive episode was made on the basis of DSM III18 symptom criteria being present at both investigations.

The data were analyzed using a computerized statistical program, SYSTAT.19 Medians (m) and 10th and 90th percentiles are given in the text for cortisol levels. A post hoc contrast analysis was used to test the mean differences between the stroke patients and the two control groups. Pearson correlation coefficients were calculated. This matrix was then applied in the factor analysis, which was performed using the principal component analysis model in SYSTAT, with varimax rotation of the factors. The multiple regression analysis was performed with the use of dummy variables (0 and 1 corresponding to no and yes, respectively) when necessary. Two-tailed t tests were used to test the regression coefficients of each independent variable against the dependent variable. A probability value of <0.05 was considered to indicate significance.

Results

Stroke patients had significantly higher basal cortisol levels (m=442, 10th and 90th percentiles 288 and 727 nmol/l, respectively) than did control patients (m=374, 232 and 562 nmol/l; F=6.1, df=1, p=0.02), but no significant difference was seen between stroke patients and the healthy elderly controls (m=450, 320 and 656 nmol/l). Morning plasma cortisol levels after dexamethasone for the stroke patients and both control groups are shown in Figure 1. Postdexamethasone plasma cortisol concentrations were significantly higher in the stroke patients than in the healthy elderly controls (F=12.5, df=1, p=0.001); concentrations were also higher in the stroke patients than in the control patients, but this difference was not significant (F=3.1, df=1, p=0.08).

By clinical and CT evaluation, 30 stroke patients were judged to have a right-sided and 32 to have a left-sided brain lesion. Forty-one stroke patients (66%) had fresh lesions visible on CT scans. Of these 41 acute stroke patients, 21 had a right-sided and 20 had a left-sided lesion. Involvement of the
different brain regions, as judged by CT, is shown in Table 1. Cerebral edema adjacent to the ischemic lesion was visualized in 15 acute stroke patients (37%), with pronounced edema in two of these 15. Old lesions were seen on CT scans in 28 (45%).

Results of the examinations regarding maximum limb paresis and orientation in the stroke patients on Day 4 after admission are shown in Figure 2. Forty-four patients (71%) had some degree of limb paresis. Seven patients (11%) were slightly drowsy at examination. Eight patients could not be scored regarding orientation due to severe dysphasia. Sixteen patients with moderate dysphasia were included in further analyses. Of the 54 patients assessable, an impairment of orientation was noted in 12 (22%).

Four patients were impossible to evaluate by DSM III criteria due to severe dysphasia and comprehension deficits. Of the 58 patients, 18 (31%) had a major depression. Major depression occurred substantially more frequently in patients with left-sided lesions (data to be published).

In the stroke patients, postdexamethasone cortisol values at 7 AM correlated significantly with those at 4 PM and 11 PM ($r=0.66$ and $r=0.35$, $p<0.001$ and $p<0.01$, respectively). In subsequent calculations, the 7 AM values were used. Three analyses were then performed for the variables potentially influencing cortisol levels. In each analysis, data were reduced to orthogonal components with a factor analysis. These factors were then included in a multiple regression analysis in an attempt to determine the independent influence of each component upon plasma cortisol levels.

The clinical variables were studied first. The eight patients with severe dysphasia (all had left-hemisphere lesions) were excluded from this analysis. The results are presented in Table 2. Right-sided brain lesion and disorientation were significantly associated with high postdexamethasone cortisol levels. Neither major depression nor pronounced limb paresis were associated with high postdexamethasone cortisol levels.

The CT variables for the stroke patients with visible fresh brain lesions were analyzed in the same way. The results are presented in Table 3. More anteriorly located lesions, that is, those with a

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**Table 1. Involvement of Cortical and Deep Structures by Computed Tomography in 41 Acute Stroke Patients**

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Right</th>
<th>Left</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal lobe</td>
<td>10</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>10</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Deep structures</td>
<td>10</td>
<td>10</td>
<td>20</td>
</tr>
</tbody>
</table>

Data are number of patients. Most patients had lesions that extended more than one brain region.

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**Table 2. Results of Multiple Regression Analysis, Using Orthogonal Scores From Factor Analysis Representing Clinical Variables, in Which Plasma Cortisol Concentration at 7 AM After Dexamethasone Is Dependent Variable**

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Standardized coefficient</th>
<th>$t$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right-sided brain lesion</td>
<td>0.34</td>
<td>2.66</td>
<td>0.01</td>
</tr>
<tr>
<td>Disorientation</td>
<td>0.29</td>
<td>2.30</td>
<td>0.03</td>
</tr>
<tr>
<td>Lowered consciousness</td>
<td>0.15</td>
<td>1.16</td>
<td>0.26</td>
</tr>
<tr>
<td>Limb paresis</td>
<td>0.11</td>
<td>0.83</td>
<td>0.42</td>
</tr>
<tr>
<td>Increasing age</td>
<td>0.10</td>
<td>0.74</td>
<td>0.45</td>
</tr>
<tr>
<td>Major depression</td>
<td>0.02</td>
<td>0.18</td>
<td>0.85</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.02</td>
<td>0.12</td>
<td>0.91</td>
</tr>
</tbody>
</table>

$n=54$; eight stroke patients were excluded from analysis due to severe dysphasia.

Probability values were obtained by two-tailed test.
shorter relative distance from the frontal pole, as well as smaller brain volumes, were associated with higher postdexamethasone cortisol levels. There was a significant inverse correlation between female sex and brain volume \((r=-0.47, p<0.01)\), as well as a negative correlation between high age and brain volume \((r=-0.35, p<0.05)\). No side difference in postdexamethasone cortisol levels could be verified.

Finally, the analysis was repeated for the 41 acute stroke patients, with the classification based on involvement of the various brain regions. The results are presented in Table 4. Frontal lobe involvement was associated with higher postdexamethasone cortisol levels, whereas involvement of the deep structures and the occipital lobe were associated with lower postdexamethasone cortisol levels.

### Discussion

We found that early after stroke, many stroke patients had a high activity in the HPA axis as measured by the dexamethasone suppression test, which has been widely used as a screening test for hypercortisolism.20 The stroke patients had a markedly higher activity than the healthy elderly controls. We found somewhat higher postdexamethasone cortisol levels (although lower than in our stroke patients) in the control patients than in our healthy elderly controls. Admission to the hospital per se may have an impact on the HPA axis, but this effect probably vanishes after the second day in the hospital.21 These data emphasize the need for adequate control groups in this type of study.

Cognitive disturbances were associated with heightened activity of the HPA axis, although we studied only one aspect of cognition (i.e., orientation). In line with our findings, cognitive impairment late after stroke has also been shown to be associated with high cortisol levels.9,12 Many CNS information-processing capabilities are supposed to be glucocorticoid-dependent22 and, based on animal studies, glucocorticoids may exert a modulatory influence on behavior.23

### Table 3. Results of Multiple Regression Analysis, Using Orthogonal Scores From Factor Analysis Representing CT Variables, in Which Plasma Cortisol Concentration at 7 AM After Dexamethasone Is Dependent Variable

<table>
<thead>
<tr>
<th>CT variable</th>
<th>Standardized coefficient</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative distance of lesion from frontal pole</td>
<td>-0.41</td>
<td>2.83</td>
<td>0.008</td>
</tr>
<tr>
<td>Brain volume</td>
<td>-0.32</td>
<td>2.19</td>
<td>0.04</td>
</tr>
<tr>
<td>Cortical atrophy</td>
<td>0.19</td>
<td>1.32</td>
<td>0.20</td>
</tr>
<tr>
<td>Right-sided lesion</td>
<td>0.17</td>
<td>1.16</td>
<td>0.26</td>
</tr>
<tr>
<td>Edema surrounding lesion</td>
<td>0.15</td>
<td>1.03</td>
<td>0.31</td>
</tr>
<tr>
<td>Anterior horn index</td>
<td>0.07</td>
<td>0.50</td>
<td>0.62</td>
</tr>
<tr>
<td>Relative lesion volume</td>
<td>0.05</td>
<td>0.37</td>
<td>0.71</td>
</tr>
<tr>
<td>Old lesions visible</td>
<td>0.02</td>
<td>0.11</td>
<td>0.92</td>
</tr>
</tbody>
</table>

CT, computed tomography. \(n=40\); analysis restricted to stroke patients with fresh lesions visible on computed tomograms. One patient was excluded due to error in CT scan computer. Probability values were obtained by two-tailed test.

### Table 4. Results of Multiple Regression Analysis, Using Orthogonal Scores From Factor Analysis Representing Involvement of Brain Regions, in Which Plasma Cortisol Concentration at 7 AM After Dexamethasone Is Dependent Variable

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Standardized coefficient</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal lobe</td>
<td>0.29</td>
<td>2.00</td>
<td>0.05</td>
</tr>
<tr>
<td>Deep structures</td>
<td>-0.29</td>
<td>2.02</td>
<td>0.05</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>-0.25</td>
<td>1.75</td>
<td>0.09</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>0.18</td>
<td>1.26</td>
<td>0.22</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>0.14</td>
<td>0.99</td>
<td>0.33</td>
</tr>
</tbody>
</table>

\(n=41\); analysis restricted to stroke patients with fresh lesions visible on computed tomograms. Probability values were obtained by two-tailed test.
Major depression that persists during the rehabilitation phase after stroke has been associated with the nonsuppressive state after dexamethasone administration in most9-12 but not all9-12 studies. Despite the high occurrence of major depression in our stroke patients (31% of those who could be evaluated), we found no association between depression and post-dexamethasone cortisol levels during the acute phase after stroke. We also analyzed depression and post-dexamethasone cortisol levels using the nonsuppression criterion defined by other investigators.4 This did not change the results; that is, the nonsuppressive state was not associated with major depression early after stroke. Note that previous studies9-12,24 examined stroke patients at variable times after the stroke event. As stroke patients may have different etiologies to their mood disorders at various times after stroke, this may be a major confounding factor.

We observed a negative correlation between activity in the HPA axis and relative distance of the brain lesion from the frontal pole. The HPA axis is substantially influenced by the CNS through the release of corticotropin-releasing hormone (CRH) from the hypothalamus. Norepinephrine influences CRH release in animal experiments.1 In rats, large areas of cortex can be deprived of noradrenergic innervation by a relatively small lesion in the frontal cortex.25 Theoretically, anteriorly located lesions could therefore profoundly affect the balance between biogenic amines and the cortisol system.

Smaller brain volumes were associated with higher HPA axis activity. It has been suggested that degenerative changes in the hippocampus, such as occur in old age, can contribute to higher activity in the HPA axis through decreased inhibition of it.26 Although these changes can be below the threshold for eliciting a disturbance of the HPA axis, an interaction with acute stress reactions, such as after acute stroke, could raise plasma cortisol concentration to excessive levels.

Stroke patients are often subject to repeated stresses (e.g., various cardiovascular complications, infections, and emotional reactions) during the disease. These repeated stresses may increase adrenal sensitivity to adrenocorticotropic hormone1 and therefore may prolong hypercortisolism as a result.

Hypercortisolism can potentially induce a cascade of negative consequences, for example, upon carbohydrate metabolism, the myocardium, and the immune system.27,28 Not surprisingly, Feibel et al9 reported greater mortality in patients with higher plasma cortisol levels and higher urinary catecholamine excretion levels.

In summary, early after stroke we found high activity in the HPA axis as measured by the dexamethasone suppression test. In a multiple regression analysis, this decreased suppressibility to dexamethasone was associated with frontally located lesions and with disorientation, but not with major depression.

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