Different Linkage of Depression to Hypercortisolism Early Versus Late After Stroke

A 3-Year Longitudinal Study

Monica Åström, MD; Tommy Olsson, MD; and Kjell Asplund, MD

Background and Purpose: Using the dexamethasone suppression test, we studied the suppressibility of the cortisol axis and its clinical determinants at various time points after stroke. A major aim was to examine the dexamethasone test as a diagnostic tool for the diagnosis of major depression in stroke patients.

Methods: The dexamethasone suppression test, major depression, functional ability, and disorientation were assessed in a cohort of 70 patients with acute stroke and after 3 months (n=63) and 3 years (n=43).

Results: Early after stroke, 24% of the patients were nonsuppressors, with about the same proportion at 3 months (22%) and 3 years (21%). None of the controls (17 healthy elderly volunteers) were nonsuppressors. High cortisol levels early after stroke were significantly associated with functional impairment (r=0.35; p=0.003) and disorientation (r=0.27; p=0.03). Three years after stroke, high postdexamethasone cortisol levels were significantly associated with major depression (r=0.57; p<0.001). The sensitivity of the dexamethasone test was 70% and the specificity 97%. In a longitudinal analysis of the long-term survivors (n=42), postdexamethasone cortisol values at 3 months predicted major depression at 3 years.

Conclusions: Hypercortisolism is associated with major depression late (3 years) but not early (0–3 months) after stroke. Patients with hypercortisolism 3 months after stroke are at risk of major depression later in the course and warrant careful follow-up from a psychiatric viewpoint. (Stroke 1993;24:52–57)

Key Words • cerebrovascular disorders • depression • dexamethasone

In earlier studies from our stroke unit we have documented the common occurrence of hypercortisolism early after stroke manifested as elevated levels of 24-hour urinary free cortisol as well as a resistance to dexamethasone suppression.1–2 Hypercortisolism is a common feature in depressive disorders,3 and the dexamethasone suppression test has thus been considered a diagnostic tool, especially in very severe, particularly psychotic depressed patients.4 We could not detect any association between hypercortisolism and major depression early after stroke.2 However, some5–8 but not all9,10 research groups have reported an association between nonsuppression to dexamethasone and poststroke depression. The specificity and the sensitivity of the test for diagnosing depression in stroke patients have been reported as highly variable;5–9,11 however, the dexamethasone test obviously has been performed at highly variable time points after the stroke event. This may have influenced the test results, as the hypothalamic–pituitary–adrenal axis may theoretically be influenced by a number of different factors at various time points after stroke.

The aim of this longitudinal study was to examine the suppressibility of the cortisol axis and its clinical determinants at various time points after stroke. A major aim was to examine the dexamethasone suppression test as a diagnostic tool for the diagnosis of major depression in stroke patients.

Subjects and Methods

In a consecutive study, 98 patients were included from the stroke unit of the Department of Medicine, Umeå University Hospital during a 12-month period. This unit admits patients directly from the emergency room who have had acute stroke for no more than 1 week.12 Sixteen patients died early after admission. One patient was not assessable because of mental retardation, and one patient refused to participate. In eight patients the dexamethasone suppression test was not performed or laboratory data were incomplete. One patient was excluded owing to a plasma creatinine level >200 μmol/l and one because of obesity (body mass index >30). Thus, 70 patients were included in the present study. There were 44 men and 26 women with a mean±SD age of 73±11 years. Of these patients, 57 had an ischemic stroke, three a cerebral hemorrhage, and 10 a transient ischemic attack. The majority (80%) were suffering from their first stroke.

No patient had high fever (>38.5°C), known extensive weight loss or malnutrition, hypothyroidism or

From the Departments of Psychiatry (M.A.) and Internal Medicine (T.O., K.A.), Umeå University Hospital, Umeå, Sweden.

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Address for correspondence: Dr. Monica Åström, Department of Psychiatry, University Hospital, S-90185 Umeå, Sweden.

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TABLE 1. Clinical Characteristics of Stroke Patients During, 3 Months After, and 3 Years After Stroke

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>During acute phase</th>
<th>Follow-up</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 Months</td>
<td>3 Years</td>
<td>3 Months</td>
<td>3 Years</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>70</td>
<td>63</td>
<td>43</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Age (mean±SD years)</td>
<td>73±11</td>
<td>73±11</td>
<td>75±11</td>
<td>75±11</td>
<td></td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>44:26</td>
<td>40:23</td>
<td>30:13</td>
<td>30:13</td>
<td></td>
</tr>
<tr>
<td>Side of brain involved</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>27 (39)</td>
<td>24 (38)</td>
<td>17 (39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>36 (51)</td>
<td>32 (51)</td>
<td>21 (49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other*</td>
<td>7 (10)</td>
<td>7 (11)</td>
<td>5 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular territory involved</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid</td>
<td>62 (89)</td>
<td>55 (87)</td>
<td>37 (86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertebrobasilar</td>
<td>7 (10)</td>
<td>7 (11)</td>
<td>6 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremity paresis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>32 (46)</td>
<td>40 (64)</td>
<td>31 (72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slight/moderate</td>
<td>20 (28)</td>
<td>11 (17)</td>
<td>8 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive</td>
<td>9 (13)</td>
<td>7 (11)</td>
<td>2 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total paralysis</td>
<td>9 (13)</td>
<td>5 (8)</td>
<td>2 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorientation</td>
<td>15/64 (23)</td>
<td>10/58 (17)</td>
<td>4/42 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depression</td>
<td>19/66 (29)</td>
<td>18/60 (30)</td>
<td>10/42 (24)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values in parentheses are percent.
* Bilateral and/or neurological symptoms such as dysarthria made side involvement uncertain.

hyperthyroidism, pituitary insufficiency, uncontrolled diabetes mellitus (no hyperglycemic or hypoglycemic coma during the year preceding the stroke), obvious abstinence reactions from alcohol or other central nervous system stimulants, or epilepsy or had medications known to possibly influence test results (e.g., glucocorticoids, estrogens, anticonvulsants, high-dose benzodiazepines, ephedrine). Fourteen of the patients (20%) had known and well-controlled diabetes mellitus.

All patients were investigated in a standardized manner, with repeated clinical assessments and computed tomographic (CT) scanning of the brain. In 45 of the patients (64%), recent brain lesions were seen. A 3-point scale for orientation was used.3 The extent of paresis (i.e., of the extremity most afflicted)4 on the fourth day after admission was quantified using a 4-point scale. Activity of daily living was recorded according to Katz et al.13 Clinical characteristics of the 70 stroke patients are given in Table 1.

The patients were investigated between the third and seventh days after admission. They were given 1 mg dexamethasone orally (Decadron, Merck Sharp & Dohme International, Rahway, N.J.) at 11 PM. Blood was drawn the following day at 7 AM, 4 PM, and 11 PM for serum cortisol analyses. A postdexamethasone cortisol level of ≥138 nmol/l at 4 PM was considered to indicate nonsuppression.14 Cortisol was analyzed with a radioimmunoassay kit from Farnos Diagnostica, Turku, Finland. The interassay coefficient of variation for the analysis was below 10%.

Stroke patients were interviewed 4–5 days after admission by the same psychiatrist, who did not know the dexamethasone values. The examinations were performed at about the same time of the day (early afternoon) to minimize the effect of diurnal mood variation. Psychiatric diagnosis of a major depression was made on the basis of DSM-III criteria (except for the organic factor criterion).15 Patients were reassessed after 10 days and at discharge as a control for stability of symptoms (modified DSM-III time criterion). When appropriate, information from relatives and staff was used to supplement patient interviews. Six patients could not be assessed regarding disorientation because of severe comprehension deficits; four of these also could not be assessed regarding depression (they could not reliably answer questions with affirmative or negative answers). All but one of these six disoriented patients died within 3 years. The surviving patient had severe comprehension deficits at 3 years and could not be assessed for either disorientation or depression. Consequently, he was not included in the longitudinal study.

Three months after the acute event the patients were reevaluated. Three patients died of recurrent stroke before follow-up, one patient refused to participate, and three patients did not undergo the dexamethasone suppression test. Thus, 63 patients remained for study. Forty-five patients were living in their homes, six were in homes for the aged, and 12 were in long-term wards. The patients were instructed to take 1 mg dexamethasone at 11 PM. The outpatients returned the following day for a physical examination and a psychiatric interview. After the examination, at about 3–4 PM, blood was drawn for cortisol analyses. Because of severe comprehension deficits, five patients could not be assessed regarding disorientation; three of these also were not assessable regarding depression.

One year after the stroke, patients were reexamined regarding major depression. Three more patients had died and two were not assessable. Thus, 61 patients were assessed.

The last follow-up was made 3 years after stroke. Since the 1-year follow-up, 12 patients had died, one had moved outside the region, and three refused to participate. Based on clinical criteria, four patients had had a recurrent stroke and were excluded, leaving forty-three patients remaining for evaluation. Thirty-four patients were living in their own homes, seven were in homes for the aged, and two were in long-term wards. The dexamethasone suppression test was performed in the same way as at the 3-month follow-up. One patient was not assessable regarding depression and disorientation because of severe comprehension deficits. During the follow-up period, three patients were treated with antidepressants in low doses (one patient with 25 mg/day nortriptyline and two with 10–20 mg/day clomipramine).

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

Control subjects were healthy volunteers who underwent physical and neuropsychiatric examinations (including CT scan). All were hospitalized during the investigations. There were eight men and nine women with a mean±SD age of 68±5 years. The dexamethasone suppression test was performed in the same way as in the hospitalized stroke group.

All analyses were made with a computerized statistical program, SYSTAT.16 Statistical calculations of mean differences between the stroke patients and the control group, adjusted for age and sex, were performed as a
multiway analysis of variance (MANOVA) and by analysis of covariance. Pearson correlation coefficients were used for the calculation of correlations. Odds ratios with their 95% confidence intervals were calculated as described by Miettinen.17 Multiple regression and discriminant function analyses were performed with the use of dummy variables (0/1 corresponding to no/yes). Thus, the Katz indexes and the orientation scale were transformed into 0/1 variables in which 1 meant any abnormality. Two-tailed \( t \) tests were used to test the regression coefficients of each independent variable against the dependent variable. A value of \( p<0.05 \) was considered significant.

Results

Cross-sectional Analysis

First week after stroke. As shown in Figure 1, none of the 17 healthy controls were nonsuppressors to dexamethasone, whereas 17 \( (24\%) \) of the 70 stroke patients were nonsuppressors \( (p=0.03 \) by Fisher's exact test). Sixty-six patients were assessed for depression. Nineteen of these \( (29\%) \) fulfilled the criteria of major depression. Of these, five \( (26\%) \) were nonsuppressors, whereas nine \( (19\%) \) of the 47 nondepressed patients were nonsuppressors (Table 2). Cortisol values at 4 PM after dexamethasone correlated significantly to the values at 7 AM and 11 PM \( (r=0.78 \) and \( r=0.63 \), respectively; \( p<0.001 \). In the subsequent analyses, the 4 PM values were used. Stroke patients had somewhat higher cortisol levels after dexamethasone than the control subjects after adjustment for age and gender \( (p=0.07 \) by MANOVA). Within the stroke group, high cortisol levels correlated significantly to functional impairment and disorientation \( (r=0.35 \) and \( r=0.27 \), giving values of \( p=0.003 \) and \( p=0.03 \), respectively) but not to major depression \( (r=0.02) \).

Three months after stroke. The number of nonsuppressors was 14 of 63 \( (22\%) \). Major depression was present in 18 of the 60 patients assessed for depression \( (30\%) \). Five of the depressed stroke patients \( (28\%) \) were nonsuppressors, whereas eight \( (19\%) \) of the nondepressed patients were nonsuppressors (Table 2). There was a significant correlation between postdexamethasone cortisol levels early after stroke and at 3 months \( (r=0.58; p<0.001) \). There were no significant correlations between postdexamethasone cortisol levels and functional impairment, disorientation, or major depression \( (r=0.23, r=0.20, \) and \( r=0.14 \), giving values of \( p=0.09, p=0.13, \) and \( p=0.31 \), respectively).

Three years after stroke. Nine \( (21\%) \) of the 43 stroke patients were nonsuppressors to dexamethasone. Major depression was present in 10 of the 42 patients assessed for depression \( (24\%) \). As shown in Table 2, the number of nonsuppressors was one of 32 \( (3\%) \) among patients without depression and seven of 10 \( (70\%) \) among patients with major depression \( (p<0.001 \) by the two-tailed Fisher's exact test). The postdexamethasone cortisol levels for patients with and without major depression are given in Figure 2. Using the conventional cut-off criterion of 138 nmol/l \( ^{14} \) gives the test a sensitivity of 70\%, a specificity of 97\%, a positive predictive value of a positive test of 88\%, a negative predictive value of 91\%, and a diagnostic accuracy of 90\%.

Postdexamethasone cortisol levels were significantly correlated with 3-month levels \( (r=0.59; p<0.001) \). Postdexamethasone cortisol levels were significantly associated with major depression \( (r=0.57; p<0.001) \) but not with functional impairment \( (r=0.28; p=0.07) \) or disorientation \( (r=0.22; p=0.17) \).

Longitudinal Analysis

In a separate analysis we restricted the study to long-term survivors, e.g., the 42 patients with data from all follow-ups. The predictive value of hypercortisolism on depression later in the course was studied. Of the 42 survivors, 33 were nonsuppressors at 3 months. Of these, three patients were depressed after 1 year and five after 3 years. Postdexamethasone cortisol levels at 3 months were positively correlated to major depression at 1 year \( (r=0.33; p=0.04) \) and at 3 years \( (r=0.50; p=0.001) \). Nonsuppression at 3 months was a statistically significant predictor of major depression at 3 years.

| TABLE 2. Association Between Dexamethasone Suppression Test Results and Major Depression in Stroke Patients at Various Time Points After Stroke |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | During acute phase \( (n=66) \) | 3 Months \( (n=60) \) | 3 Years \( (n=42) \) |
|                  | Nonsuppression | Suppression | Nonsuppression | Suppression | Nonsuppression | Suppression |
| Depressed        | 5 (26)         | 14 (74)      | 5 (28)         | 13 (72)      | 7 (70)         | 3 (30)      |
| Nondepressed     | 9 (19)         | 38 (81)      | 8 (19)         | 34 (81)      | 1 (3)          | 31 (97)     |

Values in parentheses are percent. Criterion for nonsuppression: serum cortisol level >138 nmol/l at 4 PM after 1 mg dexamethasone at 11 PM the evening before. \( n \), Number of patients.
with an odds ratio of 14 (95% confidence interval, 2.7–76.5).

Seven patients with early (0–3 months) depression recovered from depression before 1 year. Of these, all but one were suppressors at 3 months (one was a nonsuppressor throughout the follow-up period).

To take account of relations that could be overlooked by the univariate analyses, two separate discriminant function analyses were performed using age, gender, functional status and postdexamethasone cortisol values at 3 months as predictor variables and depression after 1 and 3 years as grouping variables. At 1 year the model was not significant, but at 3 years it showed significance ($\Lambda=0.73; p=0.02$; canonical correlation, 0.52). Within the model, postdexamethasone cortisol level at 3 months was the main predictor of major depression after 3 years (canonical loading, 0.95).

The determinants of postdexamethasone cortisol values at the various time points after stroke were studied in the long-term survivors by three separate standard multiple regressions. As shown in Table 3, disorientation explained about the same proportion of the variance at all time points ($p<0.19–0.23$). Functional status was most important as a determinant of postdexamethasone cortisol levels early after stroke ($p=0.09$). Three years after stroke, major depression was a significant predictor of postdexamethasone cortisol values ($p<0.001$). When the nonsuppression criterion was used, a discriminant function analysis gave the same results (data not shown); i.e., major depression was the main predictor for nonsuppression at 3 years.

**Discussion**

A negative dexamethasone suppression test (i.e., a normal suppressibility to dexamethasone) in all cases but one correctly excluded major depression in nondepressed patients 3 years after stroke. The predictive value of a negative test was 91% in this setting. A false-positive rate of 3% with this test is well in agreement with the number of false-positives in studies of healthy elderly subjects. Earlier studies of the dexamethasone suppression test in stroke patients have given highly variable results. Ross and Rush described three patients with poststroke depression, all of them nonsuppressors to dexamethasone. The sensitivity of the test has been reported to vary between 0% and 67% and the specificity between 70% and 83%. In a recent study performed in subjects at a rehabilitation center a few weeks after an acute cerebrovascular accident, the sensitivity was 100%, but the specificity in diagnosing poststroke depression was only 14%. However, the use of the dexamethasone in stroke patients has differed widely. The inclusion time has varied from 8 to 1,280 days within the same study. In other studies the inclusion time has been stated as “more than three weeks after onset” or “less than one year after onset.” Different classifications of the depressive state in stroke subjects have also been used. The present investigation is the first longitudinal study performed at well-defined time points in a population-based cohort of stroke patients.

In nonstroke patients a positive dexamethasone suppression test has been associated with major depression in 40–50% of the patients. In more severe depression with psychotic features, the sensitivity of the test has been higher, i.e., 60–70%. The specificity in nonstroke patients with major depression has varied from 70% to more than 90%. Furthermore, the dexamethasone suppression test has been said to be of limited value in patients with concomitant medical illness because a positive test is likely to be false owing to effects of medical illness on the cortisol axis. However, Lipsey et al, in a study of stroke patients somewhat younger than those in our study, found an association between major depression and nonsuppressibility to dexamethasone. The sensitivity of the test was stated as 67%, with a specificity of 70%. The total number of nonsuppressors to dexamethasone was clearly higher than that in our

**Table 3. Results From Multiple-Regression Analyses for Prediction of Serum Cortisol Levels After Dexamethasone in 42 Long-Term Survivors After Stroke**

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>During acute phase</th>
<th>3 Months</th>
<th>3 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard coefficients</td>
<td>$p$</td>
<td>Standard coefficients</td>
</tr>
<tr>
<td>Young age</td>
<td>-0.23</td>
<td>0.17</td>
<td>0.09</td>
</tr>
<tr>
<td>Female sex</td>
<td>-0.08</td>
<td>0.61</td>
<td>-0.02</td>
</tr>
<tr>
<td>Katz index (activity of daily living)</td>
<td>0.29</td>
<td>0.09</td>
<td>0.07</td>
</tr>
<tr>
<td>Disorientation</td>
<td>0.22</td>
<td>0.19</td>
<td>0.22</td>
</tr>
<tr>
<td>Major depression</td>
<td>0.10</td>
<td>0.53</td>
<td>0.14</td>
</tr>
</tbody>
</table>
A number of studies have been performed in rehabilitation units, and only one study includes outpatients. This may have influenced the test results, as hospitalization per se may influence hypothalamic–pituitary–adrenal activity.

None of the hospitalized healthy controls had a plasma cortisol level at 4 PM of >138 nmol/l; i.e., all were suppressors by conventional criteria. There is a tendency toward a decrease in the negative feedback of the hypothalamic–pituitary–adrenal axis with increasing age in various disease states, including depression. This may result from a decreased “shut-off” mechanism of this axis in old age; however, based on earlier studies from our hospital, the cut-off limit of 138 nmol/l for postdexamethasone cortisol levels seems reasonable. Claims have been made that postdexamethasone cortisol levels should be regarded as a continuous variable, especially in patients with concurrent medical illnesses.

We found a close correlation between postdexamethasone cortisol levels early after stroke and 3 months after the acute event. Repeated stresses in the period after the acute stroke event may increase adrenal sensitivity to adrenocorticotropic hormone and therefore prolong hypercortisolism, and a persistent hypercortisolism can have a number of negative effects in aged people. It has also been hypothesized that steroids themselves may be important in causing and perpetuating depression.

In our study the number of patients with major depression according to DSM-III criteria was high both early after and at 3 months after stroke. After 1 year the number of patients with major depression decreased to 10%, but at 3 years after the acute event the number increased to 24%.

The depression evolving early after stroke may theoretically be influenced by acute neuropathological changes, whereas major depression late after stroke may be related to a vulnerability of these patients induced by an earlier brain lesion. This depression late after stroke may then share similarities with major depression seen in nonstroke patients in whom hypercortisolism has been a consistent finding. It has also been suggested that chronic stress influences the later development of depression in vulnerable patients. Our data on the predictive value of high postdexamethasone cortisol levels at 3 months after stroke on the later development of major depression support this theory.

The stroke event can thus be the key event that predisposes patients to later stress activation of the hypothalamic–pituitary–adrenal axis, which in itself may contribute to the development of depression. This can be mediated through changes in the levels of corticotropin-releasing hormone in the central nervous system or an alteration of cortisol metabolites. Interestingly, treatment with steroid-suppressive drugs has recently been reported to induce a prompt remission in some depressive patients with a profound activity of the cortisol axis resistant to antidepressant therapy. This type of drug could perhaps be an alternative to antidepressive treatment in some patients for whom side effects of antidepressive drugs are a major problem.

In summary, hypercortisolism 3 months after stroke seems to predict major depression later in the course; this subgroup of patients, therefore, warrants careful follow-up from a psychiatric viewpoint. The dexamethasone suppression test had a high specificity with a lower sensitivity in detecting major depression late after stroke.

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M Aström, T Olsson and K Asplund

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