PAPER

Neuroendocrine changes in patients with acute space occupying ischaemic stroke

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Objective: To evaluate neuroendocrine changes in critical care patients with acute space occupying hemispheric stroke.
Methods: 22 patients with acute space occupying hemispheric stroke were studied (mean age 57.7 years; five women, 17 men) . Plasma levels of prolactin, thyrotropin (TSH), total thyroxine (T4), free thyroxine (FT4), and total triiodothyronine (T3) were measured on admission and thereafter on days 3, 5, 7, and 9. Cortisol and ACTH levels were analysed at 8.00, 16.00, and 24.00 hours each day. A TRH stimulation test with measurements of TSH and prolactin was done on day 3.
Results: Nine patients underwent decompressive craniectomy and nine were treated with moderate hypothermia. All patients received vasopressor drugs because of arterial hypotension. Plasma ACTH and cortisol values were abnormally low despite systemic hypotension and acute systemic illness, and remained low throughout the observation period. The diurnal rhythm of cortisol was not preserved. Prolactin levels increased during the observation period, and were well above normal on day 9. Thyroid function was slightly suppressed until day 7. TRH stimulation of plasma TSH and prolactin was low.
Conclusions: Patients with an acute space occupying cerebral infarct show profound neuroendocrine changes. The central regulation of adrenal and thyroid function and prolactin release is impaired, which may compromise the clinical course of affected patients and have implications for therapeutic management.

Neuroendocrine changes are increasingly recognised as a valid predictor of outcome in critically ill patients.[1 2] It has been suggested that changes in the hormone profile are not only adaptive but may also play a detrimental role in these patients, leading to metabolic dysregulation, impairing an adequate cardiovascular response to stress, and even augmenting cerebral oedema after head trauma.[1 3] In patients with ischaemic stroke, various studies have suggested that dysregulation at different sites within the hypothalamic-pituitary-adrenocortical axis is common and profound.[4–10] However, until now, neuroendocrine paradigms have not been evaluated in patients with large ischaemic strokes in an intensive care setting. In this study we assessed neuroendocrine changes during the first nine days in patients with space occupying hemispheric ischaemic stroke receiving neurological intensive care.

METHODS

Between August 2001 and March 2002, 22 consecutive patients with acute space occupying hemispheric strokes were included in the study (five women, 17 men; mean (SD) age, 57.7 (2.4) years). All patients were treated in the neurocritical care unit of the University of Heidelberg Hospital according to an institutional protocol for patients with space occupying infarction, including decompressive hemicraniectomy or therapeutic hypothermia as previously described.[11 12] Exclusion criteria were treatment with dopamine during the observation period (n=2), onset of symptoms omore than 12 hours before admission (n=2), and a pre-existing endocrine disorder (n=1). We measured plasma concentrations of prolactin (reference values < 15 µg/l), adrenocorticotrophic hormone (ACTH; reference values 2 to 11 pmol/l), cortisol (reference values 150 to 550 nmol/l), thyrotropin (TSH; reference values 0.2 to 3.1 mU/l), total thyroxine (T4; reference values 65 to 160 nmol/l), free thyroxine (FT4; reference values 10 to 27 pmol/l), and total triiodothyronine (T3; reference values 1.03 to 2.51 nmol/l) on admission and on days 3, 5, 7, and 9 following admission. On days 1, 3, 5, 7, and 9, ACTH and cortisol were determined at 8:00, 16:00, and 24:00 hours. All blood samples for prolactin, TSH, and the thyroid hormones were taken upon admission and thereafter at 8:00 hours through to day 9. We analysed the entire sample for differences between the three time points for each day.

ACTH was measured by a chemiluminescence immunometric assay (CLIA, Nichols Institute, San Capistrano California, USA). Cortisol was measured by a specific radioimmunoassay as previously described.[13] The other hormones were measured by using routine immunoassay procedures.

On day 3 following admission, 200 µg of protireline, a synthetic thyrotrophin releasing hormone (Relefact®, Hoechst, Frankfurt, Germany), were given slowly intravenously as a bolus dose at 8:00 hours, and blood was collected for TSH and prolactin analysis before and 30 minutes and 60 minutes after the injection. In healthy subjects, a TSH increase of 5 to 25 mU/l is considered normal, as is a three- to fivefold increase in prolactin release.[14] At each time point, a blood sample was taken through an arterial catheter in a prechilled disposable tube containing EDTA (ethylene diamine tetra-acetic acid). All blood samples were immediately centrifuged at 4°C, and the plasma obtained was frozen and stored at −32°C for further analysis. All samples were measured in the same assay. The clinical outcome was assessed on hospital discharge using the Glasgow outcome scale.

The study was approved by the institutional ethics committee. Informed consent was obtained from the patient's next of kin. The patient's anonymity was preserved in all data analyses.

Statistics

Non-parametric statistical tests (Wilcoxon signed rank and Mann–Whitney tests) were done to detect differences between each time point and the baseline values, and between the different treatment groups. Differences were considered

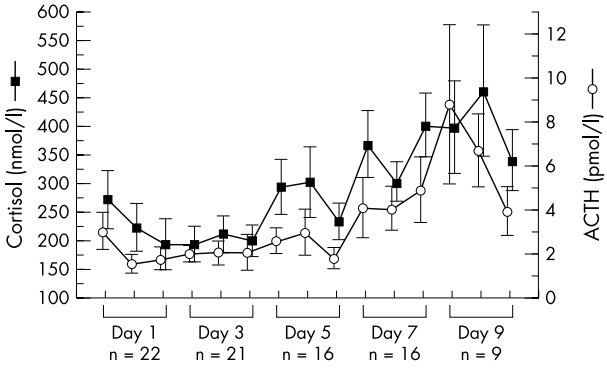

Figure 1 Plasma cortisol and ACTH concentrations in 22 patients after large hemispheric stroke. Values are means obtained at 8:00, 16:00, and 24:00 hours after admission and on days 3, 5, 7, and 9 following the stroke. Error bars = SEM. On admission and during the first few days after the stroke, plasma cortisol and ACTH values were decreased or within the lower range of normal values. Until day 9, no diurnal rhythm was present.

significant at probability (p) values of < 0.05. Data are presented as mean (SEM).

RESULTS

All 22 patients suffered from space occupying complete or subtotal infarction of the middle cerebral artery (10 right sided, 12 left sided). All patients were admitted to hospital within the first 12 hours after the onset of symptoms, and the initial blood sample for endocrine analysis was taken within this period. Nine patients with right sided infarction underwent decompressive surgery and nine were treated with therapeutic hypothermia. These patients were intubated, artificially ventilated, and treated with midazolam and fentanyl during the first four to seven days following admission. The remaining four patients received medical treatment only, without any sedative drugs. No patient received glucocorticoids.

All patients were treated with noradrenaline (norepinephrine) in variable doses to achieve a cerebral perfusion pressure of 70 mm Hg. One patient suffered from multiorgan failure following bacterial endocarditis, and 12 developed ventilator associated pulmonary infection without signs of multiorgan dysfunction.

On discharge, six patients had died of space occupying brain oedema (one of the nine patients after decompressive surgery and five of the remaining 13 non-surgically-treated patients); the remaining patients were severely disabled (GOS 3). The deaths were in one of the nine patients after decompressive surgery and in five of the remaining 13 non-surgically-treated patients. Because of death (n = 6) and transferral to other institutions (n = 7), follow up examinations were completed in 21 patients on day 3, in 16 patients on day 5 and 7, while nine patients could be examined for the full nine days.

The results of the hormone analyses are shown in figs 1 to 3. In all 22 patients, initial plasma concentrations of ACTH (mean (SEM): 3.03 (0.87) pmol/l) and cortisol (271.5 (50.8) nmol/l) were suppressed and remained low throughout the observation period (fig 1). No patient had increased plasma cortisol on admission, only two patients had slightly raised ACTH values (13.21 pmol/l and 13.43 pmol/l), and 17 of the 22 patients (77%) had ACTH values below the lower limit of the normal range (1.04 (0.10) pmol/l). In these 17 patients with low ACTH levels on admission, plasma cortisol was also low (197.8 (50.2) nmol/l). Correspondingly, nine patients (41%) had decreased plasma cortisol on admission (64.6 (16.3) nmol/l); and ACTH levels were also low in these patients (0.78 (0.10) pmol/l). ACTH and cortisol remained low throughout day 3 and 5; thereafter, there was a trend toward a return to normal values on day 7 and 9. During the first seven days, the

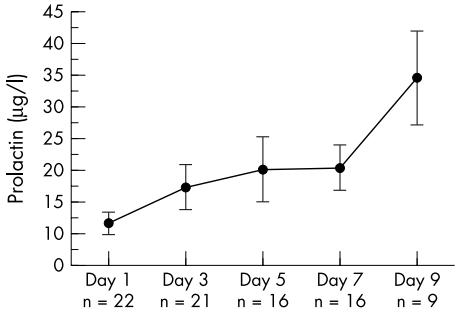

Figure 2 Mean plasma prolactin concentrations in 22 patients after large hemispheric stroke. Error bars = SEM. On admission, prolactin values were within normal limits in most patients and rose consistently throughout the observation period ($p < 0.05$).

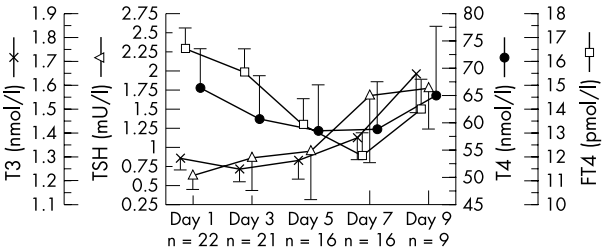

Figure 3 Mean plasma T3, TSH, T4, and free T4 (FT4) in 22 patients after large hemispheric stroke. Error bars = SEM. The changes in the different hormone levels did not reach statistical significance.

diurnal rhythm of ACTH and cortisol secretion was lost. We could not detect any significant difference between the cortisol and ACTH levels obtained at 8:00, 16:00, and 24:00 hours, except on day nine when the values obtained at 24:00 were lower than those obtained at 8:00.

Prolactin levels increased during the observation period (fig 2). On admission, four of the 22 patients (18%) had a raised plasma prolactin. On day 3, nine of 21 patients (45%) had raised values, on day 5, 10 of 16 (63%), on day 7, 10 of 16 (63%), and on day 9, all the remaining nine patients (100%) had raised values ($p < 0.05$).

The hormone levels of the pituitary-thyroid axis were normal in most patients throughout the observation period (fig 3); however, there was a trend toward a decrease in T4 and FT4 during the first seven days. T3 and TSH values remained low throughout day 5, and began to increase on day 7 and 9, respectively.

On day 3, a TRH stimulation test was done in 14 patients. In all these patients there was a blunted TSH response following TRH: TSH rose only from mean baseline values of 0.36 (0.10) mU/l to 3.16 (0.72) mU/l at 30 minutes, and 2.88 (0.82) mU/l at 60 minutes after the infusion of protireline. Prolactin rose from mean baseline values of 17.8 (4.8) µg/l to only 29.0 (7.1) µg/l 60 minutes after the protireline infusion.

Comparison between the different treatment groups (hypothermia *v* surgical treatment, and hypothermia *v* no hypothermia) revealed no significant differences. We also found no association between outcome and hormone levels.

DISCUSSION

In this study, we found low ACTH and cortisol levels on admission in patients with large hemispheric strokes, which persisted throughout the observation period. Our findings differ from the results of previous studies in stroke patients. In most of these studies, glucocorticoid levels were found to be markedly increased after stroke, and hypercortisolism was correlated with the size of the ischaemic lesion and with a

poor prognosis.[5 6 10 15 16] In one study, a diurnal rhythm of cortisol was preserved after stroke,[17] while in our patients, no diurnal rhythm was present throughout the first seven days. However, in contrast to all previous studies, our patient population consisted of critically ill patients with very large, space occupying hemispheric strokes. From this perspective, it may be surprising that the glucocorticoid concentrations—which are part of the physiological stress response—were lower in our patients with large strokes than in other unselected stroke patients. In patients with smaller strokes, hypercortisolism and an increased stress response may be a physiological response, but it seems clear that this mechanism is not maintained in the face of space occupying hemispheric infarcts. Increased intracranial pressure, with direct or indirect pressure effects on the pituitary gland, is the potential mechanism for our findings. However, during the first 24 hours after the stroke, the intracranial pressure is usually not increased; thus pressure effects cannot entirely explain the dysregulation found in our patients.

The concomitant use of midazolam and fentanyl in almost all our patients could be a possible explanation for the inadequate stress response. The influence of sedative drugs on neuroendocrine responses in the intensive care setting has not yet been sufficiently evaluated. During short term anaesthesia, both midazolam and fentanyl have been shown to reduce the stress response to major surgery.[18 19] However, there are many studies on critically ill patients after severe burns, multiple trauma, major surgery, or septic shock where a marked stress response with high levels of cortisol and ACTH were noted, despite the use of deep sedation and analgesia.[20] In animal experiments, moderate hypothermia was associated with an inhibition of ACTH release.[21] In those of our patients who were treated with mild hypothermia, we could not reproduce that result.

In critical care patients it is still controversial whether the massive neuroendocrine changes are purely adaptive and beneficial or whether they represent profound dysfunction.[1] With respect to the cardiocirculatory effects of corticosteroids, it is hard to see how downregulation of the pituitary-adrenal axis could be beneficial in our patients, because they all needed vasopressor drugs to achieve an acceptable cerebral perfusion pressure. Thus it could be speculated that cortisol replacement therapy might be useful in this particular patient population with an inadequate stress response. Moreover, because of its anti-inflammatory effects, cortisol treatment could attenuate the inflammatory response to the stroke. The distinct increase in basal prolactin concentrations and the blunted response of TSH and prolactin to TRH also support the hypothesis that low ACTH and cortisol levels indicate a dysfunctional state rather than an adaptive mechanism. In contrast to our findings in critically ill patients, in a study of 29 unselected patients with subacute stroke, free thyroxine levels were increased, and the highly variable prolactin and thyrotropin response to TRH was correlated with psychiatric findings.[8] It is known that serum prolactin concentrations increase in response to psychological or physical stress[1]; however, in our patients with an absent endogenous stress response—as indicated by low plasma ACTH and cortisol—the increased basal prolactin levels seem to indicate impaired central suprapituitary inhibition involving dopaminergic pathways. It seems unlikely that the raised prolactin was entirely caused by treatment with fentanyl and midazolam, though these drugs are known to increase prolactin levels,[22 23] because the most prominent increase in prolactin was observed at the end of the observation period when most of the patients were no longer on sedative drugs. The changes in the hormones of the pituitary-thyroid axis reflect those described in the "non-thyroidal illness syndrome" in patients who are critically ill from non-neurological disease.[24]

Conclusions

Patients with large hemispheric strokes receiving critical neurological care show profound changes in their neuroendocrine responses. In contrast to other patient populations with stroke and non-neurological disease, the central regulation of adrenal and thyroid function and prolactin release is impaired, which may compromise the clinical course of affected patients and have implications for their therapeutic management.

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