High Incidence of Neuroendocrine Dysfunction in Long-Term Survivors of Aneurysmal Subarachnoid Hemorrhage

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Background and Purpose—To investigate the incidence, pattern, and magnitude of neuroendocrine changes in long-term survivors of aneurysmal subarachnoid hemorrhage (SAH).

Methods—Thirty patients (16 women) with a mean age of 50 years underwent endocrine assessment between 12 and 24 months after aneurysmal SAH. SAH severity was graded clinically by the Hunt & Hess scale (median, II) and radiologically by the Fisher classification (median, II). Patients underwent measurement of basal hormone levels and dynamic assessment by the low-dose (1 μg) corticotropin stimulation test. Functional outcome was examined concurrently with endocrine testing by the modified Rankin Scale and the Barthel Index.

Results—Of the 30 patients tested, 14 patients (47%) showed isolated or combined endocrine abnormalities. These included low insulin-like growth factor 1 levels compatible with growth hormone deficiency in 37%, hypogonadism in 13%, and cortisol hyporesponsiveness to the low-dose corticotropin stimulation test in 10%; thyroid dysfunction in the form of subclinical hypothyroidism was observed in 7% of patients. Median modified Rankin Scale and Barthel Index at the time of endocrine testing were 1 and 100, respectively. There was no correlation between the presence of endocrine dysfunction and SAH severity indices or functional outcome scores.

Conclusions—Long-term survivors of aneurysmal SAH frequently exhibit endocrine changes, with growth hormone and gonadal deficiencies predominating. Thus, screening of pituitary function is recommended in patients surviving SAH. The relationship between late hormonal alterations and functional outcome in patients with SAH warrants further study.

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Key Words: aneurysmal ■ endocrine alterations ■ outcome ■ subarachnoid hemorrhage

It has been suggested that aneurysmal subarachnoid hemorrhage (SAH) poses a risk for hypothalamic–pituitary dysfunction, given the proximity of these structures to the arterial circle of Willis. From a theoretical point of view, endocrine disturbances may be provoked by compression of the hypothalamic–pituitary complex by the aneurysm itself, posthemorrhagic local tissue pressure changes, toxic effects of the extravasated blood, ischemia caused by vasospasm, high intracranial pressure, hydrocephalus, or local destruction during cerebral surgery. This is particularly true for aneurysms of the anterior communicating artery, the most common site of aneurysms, because arteries derived from this vessel supply portions of the hypothalamus.1 Despite these suggestions, the long-term effects of aneurysmal SAH on hypothalamic–pituitary function have received little systematic attention.2-4 Furthermore, discrepant results have been reported regarding the incidence of endocrine abnormalities, which have been found to vary widely from 11% to 50%.

Similarly, in previous studies, the pattern of hormonal impairments differs substantially, with growth hormone deficiency combined either with corticotropin (ACTH)3 or with gonadal dysfunction4 predominating.

Studies following-up patients who have survived SAH have noted relatively high rates of functional limitations along with quality-of-life impairment, such as fatigue, decreased mobility, loss of motivation, abnormally low independence, and participation on measures of social functioning, even in those patients making good neurological recovery.4,5 The cause of these functional problems remains, at least in part, unclear. Of interest, many of these symptoms are similar to those occurring in patients with untreated hypopituitarism.6

The primary aim of this study was to further clarify the rate, pattern, and severity of endocrine abnormalities after aneurysmal SAH. Furthermore, we sought to investigate the potential associations between hormonal changes and func-
tional outcome in SAH patients. To this end, 30 long-term survivors of SAH underwent basal hormone evaluation and dynamic assessment with the low-dose (1 μg) ACTH stimulation test.7

Materials and Methods

Study Population
All consecutive patients with aneurysmal SAH admitted in the Department of Neurosurgery over a 2-year period (between 2002 and 2003) were enrolled in the study. Inclusion criteria consisted of a time window of SAH of >12 months but <24 months before endocrine testing. Exclusion criteria included treatment with drugs affecting the hypothalamic–pituitary function, a pre-existing endocrine disorder, and liver or renal failure.

The Institutional Review Board approved the study. Informed consent was obtained from all patients.

Data Collection
The following variables were recorded in all patients: age, sex, clinical severity on admission to the hospital by the Hunt & Hess grading system,8 radiological severity of bleeding seen on brain computed tomography scan by the Fisher classification,9 aneurysm location, treatment modality (surgery or embolization), and whether intensive care unit hospitalization along with mechanical ventilatory support were required. SAH-related complications, such as vasospasm, intraoperative rupture, hydrocephalus, rebleeding, high intracranial pressure, or epileptic seizures, were also noted.

Endocrine Evaluation
Morning endocrine testing was performed between 8:00 and 8:30 AM and included the measurement of the following hormones: cortisol, ACTH, dehydroepiandrosterone sulfate (DHEAS), free thyroxine (fT4), tri-iodothyronine, thyroid-stimulating hormone (TSH), testosterone in men, estradiol in women, follicle-stimulating hormone, luteinizing hormone (LH), prolactin (PRL), growth hormone (GH), and insulin-like growth factor-1 (IGF-1). Immediately after, a low-dose ACTH stimulation test was performed: 1 μg of freshly prepared tetracosactin (Synacthen; Novartis) was injected as an intravenous bolus, and 30 minutes later a second blood sample was obtained to measure stimulated cortisol levels.

Definitions of Endocrine Abnormalities
Endocrine abnormalities were defined as follows: (1) cortisol hyporesponsiveness was considered if stimulated cortisol was <18 μg/dL after the low-dose ACTH stimulation test;10 (2) thyroid dysfunction was defined as primary hypothyroidism (subnormal serum fT4 in association with high TSH) or subclinical hypothyroidism (mildly elevated serum TSH along with normal levels of serum fT4);11 (3) in association with high TSH) or subclinical hypothyroidism (mildly elevated serum TSH along with normal levels of serum fT4);11 (4) levels of IGF-1 lower than 2 standard deviations for elevated serum TSH along with normal levels of serum fT4);11 (3) in association with high TSH) or subclinical hypothyroidism (mildly elevated serum TSH along with normal levels of serum fT4);11 (4) levels of IGF-1 lower than 2 standard deviations for the appropriate age range were considered as indicating inadequate GH secretion.13 In addition to the aforementioned endocrine abnormalities, the following abnormal hormone levels were also recorded: high PRL and low DHEAS.

Functional Outcome Evaluation
The modified Rankin Scale (MRS) and the Barthel Index (BI) assessed functional outcome concurrently with endocrine testing. The MRS investigates the level of disability and includes a comparison to previous activities. This scale defines 5 levels of disability, ranging from no symptoms at all (score, 0) to severe disability (score, 5), and one score for death (score, 6).14 MRS 6 is not included in the analysis because the present study focuses on the outcome among SAH survivors.

The BI places weight on activities of daily living and comprises 10 items, which can be divided into a group related to self-care (feeding, grooming, bathing, dressing, controlling bowels and bladder, and toilet use), and a group related to mobility (ambulation, transfers, and stair climbing). The BI is a cumulative score calculated by summing each item score. The scores are multiples of 5, with a range of 0 (completely dependent) to 100 (independent). Higher scores represent a higher degree of functional independence.15

Statistical Analysis
Variables were checked for normality with the Kolmogorov–Smirnov test. Data are presented as the mean ± SD of the mean, or as medians. Pearson or Spearman correlation coefficients assessed the relationships between variables. Comparisons between groups were performed by unpaired t test, Mann–Whitney rank sum test, χ² analysis, or Fisher exact test as appropriate. Differences were considered significant at P<0.05.

Results

Study Population
During the study period, 30 patients with aneurysmal SAH fulfilled the inclusion criteria and were thus enrolled in the current study. There were 16 women (11 postmenopausal and 5 premenopausal) and 14 men with a mean age of 50±13 years (range, 20 to 71 years) at the time of endocrine evaluation. On admission in the hospital, Hunt & Hess grading ranged from I to IV (median, II), and Fisher classification ranged from I to IV (median, II). Aneurysms involved the anterior communicating artery (n=13), the middle cerebral artery (n=6), the internal carotid artery (n=5), the posterior cerebral artery (n=3), the posterior communicating artery (n=2), and the basilar artery (n=1). Treatment included embolization (n=20) or surgical clipping (n=10). Nine patients were admitted to the intensive care unit requiring mechanical ventilatory support. Overall, 7 patients exhibited 8 complications, including vasospasm (n=4), epileptic seizures (n=2), hydrocephalus (n=1), or intraoperative rupture (n=1).

Endocrine Assessment: Functional Outcome
Median or mean hormone levels and the corresponding ranges of the 30 SAH long-term survivors, along with the local reference values, are shown in Table 1. Fourteen (47%) patients had an abnormal result in at least one hormonal axis tested. These included low IGF-1 levels (n=11 or 37%), hypogonadism (n=4 or 13%), cortisol hyporesponsiveness (n=3 or 10%), and subclinical hypothyroidism (n=2 or 7%). Endocrine abnormalities were single (n=10), dual (n=2), or triple (n=2). The clinical characteristics of these 14 patients, such as age, gender, clinical and radiological SAH severity, aneurysm location, and treatment modality, are shown in Table 2. Patients 1, 11, and 13 had cortisol hyporesponsiveness; baseline and stimulated cortisol ranged from 5 to 10 μg/dL and from 15 to 16 μg/dL, respectively. Patients 2, 3, 5, and 7 to 14 had low IGF-1 levels, ranging from 10 to 163 ng/mL. Two men, patients 1 and 11, had hypogonadism, with testosterone one levels of 123 and 254 ng/dL, respectively. Two postmenopausal women, patients 4 and 8, had low follicle-stimulating hormone levels (13.7 and 10.2 mIU/mL, respectively). LH concentrations in these 2 women were...
Within normal ranges (9.6 and 7.2 mIU/mL, respectively). Patients 6 and 8 had subclinical hypothyroidism; their thyroid function testing results were: tri-iodothyronine/H11005167 and 104 ng/dL, fT4 = 1.0 and 1.10 ng/dL, and TSH = 7.38 and 6.04 IU/mL, respectively. In addition to these endocrine abnormalities, the following abnormal hormone levels were noted: 7 patients, 5 males and 2 females, had mild hyperprolactinemia (PRL ranged from 12.7 to 59.5 ng/mL), and 11 patients had low DHEAS for their age, ranging from 304 to 786 ng/dL.

Long-term functional evaluation revealed that SAH patients had mainly recovered. Median MRS was 1 (range: 0 to 2), and its distribution was MRS 0 (n=7), MRS 1 (n=17), and MRS 2 (n=6). Median BI was 100; BI was <100 only in 5 patients, ranging from 60 to 95.

The comparison of SAH patients with normal endocrine function to those with endocrine abnormalities (ie, those having cortisol hyporesponsiveness to the low-dose ACTH stimulation test, thyroid function abnormalities, low IGF-1 levels, or hypogonadism) is shown in Table 3. The 2 groups were similar with regard to age, gender, clinical state on admission in the hospital, severity of bleeding on brain computed tomography scan, incidence of aneurysm located in the anterior communicating artery, treatment modality, incidence of postoperative complications, and intensive care unit hospitalization. Furthermore, the 2 groups had comparable outcome scores (MRS and BI). None of the hormones correlated with SAH severity indices or functional outcome scores.

Discussion
Evidence that aneurysmal SAH might be associated with neuroendocrine dysfunction comes mainly from case reports\textsuperscript{16–19} or small series of patients.\textsuperscript{20} Systematic studies...
investigating this issue are limited in number and have yielded conflicting results. In 1975, Osterman investigated 50 patients 3.5 months after SAH. The hypothalamic–pituitary–adrenal axis was assessed by the circadian rhythm of plasma 11-hydroxycortisol and the metyrapone test. Thyroid and gonadal function were evaluated clinically and by the corresponding baseline hormones. He found that endocrine abnormalities were rare; 6% of the patients had an abnormal circadian rhythm in cortisol, 11% had a pathological metyrapone test, 2% had mild thyroid function abnormalities, whereas hypogonadism was not present. A subsequent study investigated 21 patients between 14 and 43 months after SAH. Pituitary function was investigated by a combined thyrotropin-releasing hormone–luteinizing hormone-releasing hormone arginine test and the insulin tolerance test. Contrasting the results of Osterman, this study showed that 43% of the patients screened showed isolated or combined endocrine abnormalities; these included ACTH (n = 4) or GH deficiency (n = 3) and ACTH plus GH impairment (n = 2). A recent study assessed a small number of patients (10 subjects) 1 year after SAH by routine laboratory investigation and by dynamic tests. A significant number of patients (50%) had some degree of diminished pituitary capacity. Abnormalities consisted of isolated or combined gonadotroph and somatotroph deficiencies, whereas adrenal and thyroid functions were preserved in all cases.

In concordance with the most recent of the aforementioned studies, in the present study we found, in a larger cohort of patients, that endocrine abnormalities are common in survivors of SAH, affecting 47% of the patients screened. The most common alteration in our series was a diminished secretion of GH, as reflected by the finding of low IGF-1 levels in a substantial proportion of our patients. Although a dynamic assessment of GH reserve is usually recommended for assessing somatotroph function, there is now good evidence that low IGF-1 concentrations represent a good marker of GH deficiency. Hypogonadism, evaluated by widely accepted diagnostic criteria, was the second most common deficiency observed in this study. The adequacy of cortisol was assessed by dynamic testing. For this purpose, the low-dose (1 μg) ACTH stimulation test was used. This test correlates closely with the insulin-induced hypoglycemia test, the generally agreed reference standard for the evaluation of the hypothalamic–pituitary–adrenal axis, and seems to be superior to the high-dose ACTH test in detecting subtle defects of adrenal reserve. Although a diminished cortisol response was observed in only 3 patients, this finding is of paramount importance because unrecognized cortisol deficiency may have serious consequences if the patient has to cope with a stressful situation. Finally, the thyroid abnormalities observed in 2 patients of this study demonstrated a pattern compatible with subtle primary thyroid failure; therefore, we presume that this finding is not related with a central defect of the anterior pituitary thyrotroph cell function.

### TABLE 2. Characteristics of the 14 Patients With Endocrine Abnormalities Surviving Aneurysmal Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>Aneurysm Location</th>
<th>H &amp; H Location</th>
<th>Fisher Grade</th>
<th>TT</th>
<th>Hormonal Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>39</td>
<td>AcoA</td>
<td>II</td>
<td>II</td>
<td>Surg</td>
<td>C Low testosterone</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>60</td>
<td>ICA</td>
<td>II</td>
<td>IV</td>
<td>Surg</td>
<td>Low IGF-1</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>20</td>
<td>MCA</td>
<td>I</td>
<td>II</td>
<td>Emb</td>
<td>Low IGF-1</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>50</td>
<td>MCA</td>
<td>I</td>
<td>II</td>
<td>Surg</td>
<td>Low FSH</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>57</td>
<td>MCA</td>
<td>I</td>
<td>II</td>
<td>Surg</td>
<td>Low IGF-1</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>67</td>
<td>AcoA</td>
<td>III</td>
<td>III</td>
<td>Emb</td>
<td>High TSH</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>37</td>
<td>PCA</td>
<td>I</td>
<td>I</td>
<td>Emb</td>
<td>Low IGF-1</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>48</td>
<td>MCA</td>
<td>I</td>
<td>I</td>
<td>Surg</td>
<td>Low IGF-1</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>53</td>
<td>AcoA</td>
<td>III</td>
<td>II</td>
<td>Emb</td>
<td>Low IGF-1</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>51</td>
<td>PcoA</td>
<td>III</td>
<td>II</td>
<td>Surg</td>
<td>Low IGF-1</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>53</td>
<td>AcoA</td>
<td>I</td>
<td>II</td>
<td>Emb</td>
<td>Low testosterone</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>37</td>
<td>MCA</td>
<td>II</td>
<td>II</td>
<td>Emb</td>
<td>Low IGF-1</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>55</td>
<td>PcoA</td>
<td>II</td>
<td>II</td>
<td>Emb</td>
<td>Low IGF-1</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>57</td>
<td>ICA</td>
<td>II</td>
<td>I</td>
<td>Emb</td>
<td>Low IGF-1</td>
</tr>
</tbody>
</table>

H & H indicates Hunt and Hess; TT, treatment; AcoA, anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; PcoA, posterior communicating artery; Surg, surgery; Emb, embolization; CH, cortisol hyposresponsiveness; IGF-1, insulin-like growth factor 1; FSH, follicle stimulating hormone; TSH, thyrotropin-stimulating hormone; M, male; F, female.
TABLE 3. Comparison of SAH Survivors With Normal Endocrine Function to Those With Hormonal Abnormalities

<table>
<thead>
<tr>
<th></th>
<th>Patients With Normal Endocrine Function (n=16)</th>
<th>Patients With Endocrine Abnormalities (n=14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>50±15</td>
<td>49±12</td>
<td>0.81</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, no.</td>
<td>10</td>
<td>4</td>
<td>0.14</td>
</tr>
<tr>
<td>Female, no.</td>
<td>6</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Hunt &amp; Hess score†</td>
<td>2</td>
<td>2</td>
<td>0.55</td>
</tr>
<tr>
<td>Fisher classification†</td>
<td>2</td>
<td>2</td>
<td>0.07</td>
</tr>
<tr>
<td>AcoA, no.</td>
<td>9</td>
<td>4</td>
<td>0.25</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embolization, no.</td>
<td>12</td>
<td>8</td>
<td>0.44</td>
</tr>
<tr>
<td>Surgery, no.</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Complications, no.</td>
<td>2</td>
<td>5</td>
<td>0.20</td>
</tr>
<tr>
<td>ICU hospitalization, no.</td>
<td>3</td>
<td>6</td>
<td>0.24</td>
</tr>
<tr>
<td>Modified Rankin Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, no.</td>
<td>3</td>
<td>4</td>
<td>0.69</td>
</tr>
<tr>
<td>1, no.</td>
<td>9</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>2, no.</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Barthel Index†</td>
<td>100</td>
<td>100</td>
<td>0.21</td>
</tr>
</tbody>
</table>

SAH indicates subarachnoid hemorrhage; AcoA, anterior communicating artery; ICU, intensive care unit.

*Mean±SD.
†Median values.

Of interest, the pattern of neuroendocrine dysfunction observed in our study is very similar to that described in patients with other pathological conditions of the central nervous system, such as in long-term survivors of head trauma or after brain irradiation. These data indicate that GH and/or gonadotropin function are more fragile compared with the other axes, and that the pattern of endocrine abnormalities is unrelated to the type of brain injury. The hormonal abnormalities observed in the current study must be considered as permanent, because the time interval between the acute event and endocrine evaluation was sufficiently long to allow patients to reach a steady-state; this, in turn, suggests that such patients should be closely monitored for possible future deterioration.

The pathophysiology underlying the endocrine abnormalities after SAH remains undetermined. The present study does not elucidate whether there is a predominant involvement of the hypothalamus or the pituitary. However, the presence of hyperprolactinemia in a certain percentage of our unstressed patients (23%) is best explained by an injury to the hypothalamus that disrupts its normal inhibition of prolactin secretion by the pituitary lactotrophs. The concept of a hypothalamic cause for hormone deficiency after SAH is also supported by a recent functional study showing reduced cerebral blood flow in the central suprasellar region and by pathology data demonstrating ischemic necrosis along with hemorrhage in the hypothalamus. In this study, aneurysms of a varying distribution in the cranial vault were associated with some endocrine dysfunction; therefore, it is presumed that hormonal abnormalities in these patients occurred as a result of the SAH insult. However, there is also a possibility that unruptured aneurysms of the circle of Willis, in close proximity with the hypothalamic–pituitary unit, may interfere with neuroendocrine function. A study investigating the integrity of neuroendocrine function of such patients with unruptured aneurysms is required to clarify this issue.

In the current study, we failed to identify any factors posing a risk for endocrine changes after aneurysmal SAH. Similarly, we were unable to demonstrate any associations between late hormonal changes and disability or activities of daily living. This could be related to the fact that the sample size is relatively small and compromises the interpretation of the statistical tests; thus, our results must be considered as preliminary. Clearly, further investigation involving a larger cohort is warranted to better elucidate these important issues.

Summary

Our data suggest that endocrine abnormalities are common in long-term survivors of aneurysmal SAH. Thus, SAH should be added to the list of the causes of adult-onset hypopituitarism, which includes cerebral tumors, pituitary infarction or surgery, head trauma, brain irradiation, and other rare entities.

References

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