OBJECTIVE: The hypothalamic-pituitary-adrenal axis is an important part of the body’s natural response to acute illness. Adrenal insufficiency has the potential to lead to hemodynamic instability and electrolyte imbalances, limit the body’s ability to respond to stress, and worsen overall clinical outcome. In this case series, we describe 16 patients evaluated for acute adrenal insufficiency after aneurysmal subarachnoid hemorrhage.

CLINICAL PRESENTATION: Over a 2-year period, the medical records of 16 patients admitted to the adult neurosurgery service for aneurysmal subarachnoid hemorrhage who were nonresponsive to vasopressor therapy and received cosyntropin for the evaluation of adrenal insufficiency within 14 days of their event were reviewed.

INTRODUCTION: The median baseline cortisol in this population was 22.5 μg/dL, with a poststimulation cortisol level of 31 μg/dL. Of the population surveyed, a total of 11 patients met the preestablished criteria for adrenal insufficiency, 3 with baseline cortisol levels of less than 15 μg/dL and 11 with poststimulation concentration changes of less than 9 μg/dL. Baseline serum cortisol concentrations were significantly correlated with hospital stay (P = 0.045), intensive care unit stay (P = 0.005), and ventilator days (P = 0.006).

CONCLUSION: To date, this is the only investigation evaluating the incidence of acute relative adrenal insufficiency in this population. In our cohort, 69% of the patients met the preestablished criteria for relative adrenal insufficiency. The impact of low-dose corticosteroid therapy in this population also needs review, as it could have significant implications for the management of cerebral vasospasm.

KEY WORDS: Adrenal insufficiency, Aneurysmal subarachnoid hemorrhage, Brain injury, Steroids
ciency in the acute setting has not been evaluated in the literature in patients with aneurysmal SAH.

Aneurysmal SAH affects approximately 27,000 people each year (8). Cerebral vasospasm, a known sequela of aneurysmal SAH, is characterized by severe vasoconstriction of the major intracerebral arteries, potentially resulting in ischemic complications. Current pharmacological treatment is aimed at optimizing hemodynamic status by promoting hypervolemia, hypertension, and hemodilution (triple-H therapy). In addition, hyponatremia, associated with adrenal insufficiency could be detrimental in the treatment of patients with aneurysmal SAH. Identification of this as a complication of this disease would help health care providers in treating this often devastating entity. Currently, there are no studies evaluating the incidence of adrenal insufficiency in the setting of aneurysmal SAH, and only 1 case report has documented the impact of low-dose corticosteroid therapy in this population (3).

The purpose of this investigation was to determine the incidence of acute relative AI in patients with aneurysmal SAH who are unresponsive to vasopressor therapy. Secondary outcome measures were to correlate the presence of AI and clinical outcome and to assess improvement with corticosteroid treatment in those patients identified.

PATIENTS AND METHODS

From a searchable pharmacy database, the medical records of patients older than 18 years who had been admitted to the Adult Neurosurgery Service at the University of North Carolina Hospitals for aneurysmal SAH from November 2004 through December 2006, and who had been prescribed cosyntropin, were reviewed retrospectively. Patients who were pregnant at the time of their event, had preexisting AI or pituitary insufficiency, received glucocorticoids in the perioperative setting, or received glucocorticoids within 3 months before their injury were excluded.

Patients who demonstrated blood pressures unresponsive to vasopressor therapy (as defined by the necessity of repeated fluid replacement and multiple or increasing vasopressor requirements for >24 hours) were evaluated for inclusion based on the clinical judgment of the treating physician. Relative AI secondary to aneurysmal SAH was defined as a baseline cortisol level of less than 15 μg/dL or a change of less than 9 μg/dL after a 1-μg cosyntropin stimulation test within the first 14 days of their causal event (11, 24, 28). The primary endpoint was to observe the number of patients admitted with aneurysmal SAH who, after testing, were determined to have relative AI. Data were collected regarding baseline characteristics (age, sex, race, Fisher grade, and Hunt and Hess grade) to determine whether there were any predisposing or contributing factors. Medication data were collected to determine whether either etomidate or other metabolic suppressive agents (e.g., pentobarbital and propofol) were used that may have contributed to adrenal suppression (10). Secondary endpoints were to determine whether this condition, and/or its treatment, had effects on mean arteriolar pressure, vasopressor requirements, intensive care unit (ICU) stay, hospital stay, ventilator-dependent days, or mortality compared with those who did not exhibit relative AI. To assess infectious risk, data were also collected to detect any increase in the number of positive cultures among those patients who received steroids.

Descriptive statistics were used to report demographic and baseline data comparisons. All data are expressed as median (range) and percentiles of the total sample, unless otherwise stated. Statistical analysis of the data was completed using SigmaStat 3.5 software (SyStat Software, Inc., Point Richmond, CA). Student’s t test and the Mann-Whitney U test were used to assess quantitative variables and z tests were used to compare qualitative variables. Cortisol concentration values were compared to continuous data using simple linear regression. Multiple logistic regression analysis was used to assess correlations between variables. Significance was defined as a P value less than 0.05.

RESULTS

Eighty-seven patients were admitted with aneurysmal SAH during the study period, 16 of whom met the inclusion criteria. Demographic criteria are listed in Table 1. The median baseline cortisol in this population was 22.5 μg/dL, with a poststimulation cortisol level of 31 μg/dL. In the population surveyed, 11 patients met the preestablished criteria for AI, 3 with baseline cortisol levels of less than 15 μg/dL and 11 with poststimulation concentration changes of less than 9 μg/dL. The median timing of AI evaluation was 5.5 days (range, 2–12 d) from ictus. Of these 11 patients, 8 received low-dose corticosteroid therapy

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr)/sex</th>
<th>Race and Hess grade</th>
<th>Fisher grade</th>
<th>Aneurysm treatment</th>
<th>Albutin (g/dL)</th>
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<tr>
<td>1</td>
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<td>4</td>
<td>Clip</td>
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</tr>
<tr>
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<td>74/F</td>
<td>Other</td>
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<td>Clip</td>
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<tr>
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<tr>
<td>16</td>
<td>54/F</td>
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</table>
(100 mg intravenously every 8 hours). Two other patients also received steroid therapy despite not meeting preestablished criteria. The median duration of steroid therapy was 8 days (range, 2–19 days). Percentages of patients meeting different definitions of relative AI are depicted in Fig. 1. A total of 10 patients received some form of adrenal suppressive therapy surrounding their adrenal evaluation. There were no significant differences between those who were and were not classified as having AI with regard to medications that may alter adrenal response (Table 2).

Secondary endpoints and details regarding aneurysmal SAH severity are listed in Table 3. The mortality rate in those patients receiving steroids was 30% (n = 3) compared with 66% (n = 4) in the nonsteroid group (P = 0.376). Baseline cortisol was positively correlated with mortality (odds ratio, 1.210; 95% confidence interval, 0.926–1.580; P = 0.163), whereas increasing number of steroid days was negatively associated with mortality (odds ratio, 0.725; 95% confidence interval, 0.518–1.016; P = 0.062), although neither reached statistical significance. Baseline serum cortisol concentrations were significantly correlated with hospital stay (P = 0.045), ICU stay (P = 0.005), and ventilator days (P = 0.006). Poststimulation cortisol concentrations were also significantly correlated with hospital stay (P < 0.007), ICU stay (P < 0.001), and ventilator days (P < 0.001). Intracranial pressure was also significantly higher in those with lower poststimulation levels (P = 0.04). An inverse association was noted between the duration of ventilation and the length of steroid therapy (P = 0.04). There were no significant differences in intracranial pressure (P = 0.712), cerebral perfusion pressure (P = 0.878), mean arterial pressure (P = 0.926), or vasopressor dose (P = 0.515) before and after the use of steroids. There was also no significant difference noted in the development of positive microbial cultures between the steroid-treated and non-steroid-treated groups (P = 0.674).

**DISCUSSION**

To our knowledge, this is the first investigation to attempt to quantify the incidence of acute relative AI secondary to aneurysmal SAH and the largest to evaluate the effects of low-dose corticosteroid use in this population. In the population reviewed, 69% of the patients met the preestablished criteria for relative AI. Serum cortisol levels were also demonstrated to correlate significantly with ICU stay, hospital stay, and ventilator-dependent days.

The treatment of relative AI is included in the Society of Critical Care Medicine’s Surviving Sepsis Campaign guidelines as a therapeutic modality with which to decrease mortality related to septic shock (13, 14). According to the 2003 guidelines, the recommendation for diagnosis of this condition is the use of a 1- or a 250-μg cosyntropin stimulation test and a subsequent postcosyntropin change in baseline cortisol levels of less than 9 μg/dL. Some authors have suggested that a random cortisol level of less than 15 to 25 μg/dL could provide evidence of relative AI in the setting of critical illness, regardless of the cortisol change after cosyntropin stimulation (11, 24, 28). The recommendation for the treatment of this condition involves the use of hydrocortisone (<300 mg/day), with the optional addition of fludrocortisone (50 μg/day) (13, 14).

Although the evaluation of adrenal function has become a routine clinical practice in the setting of septic shock, its use in the field of brain injury is a more recent development. Cohan et al. (10) found that approximately 50% of patients with moderate or severe traumatic brain injury had at least transient AI. Bernard et al. (6) suggested that this incidence may be as

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**TABLE 2. Adrenal suppressive therapies**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Steroid-treated group</th>
<th>Non-steroid-treated group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etomidate</td>
<td>1</td>
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<td>0.631</td>
</tr>
<tr>
<td>Propofol</td>
<td>2</td>
<td>3</td>
<td>0.486</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>1</td>
<td>1</td>
<td>0.693</td>
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</tbody>
</table>

**TABLE 3. Secondary endpoints**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Steroid-treated group</th>
<th>Non-steroid-treated group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunt and Hess score, mean (SD)</td>
<td>3.1 (0.9)</td>
<td>2.8 (1.2)</td>
<td>0.610</td>
</tr>
<tr>
<td>Fisher grade, mean (range)</td>
<td>4.0 (2–4)</td>
<td>3.5 (1–4)</td>
<td>0.611</td>
</tr>
<tr>
<td>Vasopressor days, mean (SD)</td>
<td>9.2 (5.8)</td>
<td>8.1 (5.4)</td>
<td>0.728</td>
</tr>
<tr>
<td>Hospital stay, mean (range)</td>
<td>18 (10–39)</td>
<td>22 (8–42)</td>
<td>1.0</td>
</tr>
<tr>
<td>Intensive care unit stay, mean (range)</td>
<td>13 (9–24)</td>
<td>18 (9–42)</td>
<td>0.870</td>
</tr>
<tr>
<td>Ventilator-dependent days, mean (SD)</td>
<td>10 (6.5)</td>
<td>22 (15.5)</td>
<td>0.058</td>
</tr>
</tbody>
</table>

*SD, standard deviation.*
high as 100%. Currently, the duration of this effect also remains in question, but evidence suggests that it may persist for months after injury (2). As a result, some authors have gone as far as to recommend the universal evaluation of basal hormonal testing in patients with SAH, in moderate to severe TBI, and in all cases of TBI with clinical symptoms suggestive of hypopituitarism (33). Multiple autopsy studies have documented the existence of acute pituitary necrosis in up to one-third of fatal head injury victims (1, 10, 12). These results have prompted the question of the possibility of this disorder’s being present in the setting of aneurysmal SAH and cerebral vasospasm.

First documented nearly 50 years ago, cerebral vasospasm can be a devastating consequence of aneurysmal SAH (18). It is defined as a critical narrowing of the major cerebral arteries and has been observed to occur in 20 to 70% of patients with aneurysmal SAH, usually within 3 to 7 days of the hemorrhagic ictus (21, 29, 34). Ischemia progressing to infarction is observed in approximately one-quarter of patients who exhibit clinical signs of vasospasm. The exact pathophysiology underlying vasospasm after aneurysmal SAH has not been clearly elucidated. Multiple studies demonstrate that the presence of hemorrhage in the subarachnoid space induces a biochemical cascade that acts to alter the contractility of cerebral vessels, influence cerebral edema, and alter cerebral blood flow, resulting in ischemic sequelae (9, 16, 17, 23, 26, 27, 30–32). No clear correlation appears to exist between vasospasm and hormonal disruption. However, studies have demonstrated that aneurysmal SAH may induce alterations in the hypothalamic-pituitary-adrenal axis (22). These alterations may then induce dysfunction in the brain’s ability to address the abnormal cerebral blood flow, vessel contractility, blood-brain barrier disruption and associated vasogenic edema, and metabolic disruptions that may then act to further exacerbate the sequelae of cerebral vasospasm. To date, only one other investigation has documented the existence of relative AI in the setting of aneurysmal SAH. In 2001, Alhashemi (3) reported the case of a 67-year-old woman with vasospasm secondary to aneurysmal SAH who had a baseline serum cortisol concentration of 20 μg/dL on Day 14. After the initiation of hydrocortisone (100 mg intravenously every 8 hours), the patient was noted to have a significant reduction in vasopressor requirements.

The results of this study are largely limited by the small population and by its retrospective nature. Although no patient presented with a previous diagnosis of AI, it is possible that some patients may have had this as an underlying condition. Also, at this institution, free serum cortisol concentration measurement, a potentially more accurate marker of hypothalamic-pituitary-adrenal axis activity in the setting of acute illness, is unavailable (5). However, serum albumin concentrations were collected and only 1 patient had a concentration of less than 2 g/dL, the level below which the percentage bound is noted to be reduced (20). The identification of approximately two-thirds of these patients as having AI is of potential marked clinical significance. AI has the potential to further hinder the treatment of cerebral vasospasm, which already accounts for a significant degree of morbidity and mortality in patients with aneurysmal SAH. If an increased incidence of this entity truly exists, there may be a role for early diagnosis and potential treatment. It is reasonable to screen aneurysmal SAH patients who demonstrate signs and symptoms of AI early in their stay, particularly those refractory to vasopressor therapy. The results of this analysis also suggest that serum cortisol concentration may be a potential marker of severity of illness in this setting and may provide some prognostic value.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials or devices described in this article.

CONCLUSION

This study, although preliminary in nature, may provide a basis for future investigations to assist in the treatment of aneurysmal SAH. These studies should focus on determining the appropriate laboratory or clinical diagnostic criteria for this condition, as well as the appropriate method and benefits of treatment.

REFERENCES


ADRENAL INSUFFICIENCY INANEURYSMALSUBARACHNOID HEMORRHAGE


COMMENTS

This provocative article suggests that many patients with aneurysmal subarachnoid hemorrhage (SAH) have adrenal insufficiency (AI). Only a selected subset of patients was studied, the definition of AI is variable, and the numbers here are small. Thus, it is not possible to accurately state the incidence of AI after SAH on the basis of these data. The need for vasopressors to maintain blood pressure could be due to AI as well as to myocardial dysfunction and other reasons. “A total of 10” (why not just “10?”), patients got medication that could suppress adrenal function. Nevertheless, the incidence does not matter as this article raises an important diagnosis. This diagnosis requires further study because, in the aneurysm rupture phase, we are behind in comparison to similar investigations in other areas of neurosurgery such as head injury.

R. Loch Macdonald
Toronto, Canada

Want et al. have put together a case series of 16 patients evaluated for acute AI after aneurysmal SAH. Each patient was nonresponsive to vasopressor therapy and received cosyntropin for the evaluation of AI. Eleven of these patients met the criteria for AI, with baseline serum cortisol concentrations being significantly correlated with hospital stay, intensive care unit stay, and ventilator days. The authors concluded that corticosteroid therapy in patients with aneurysmal SAH needs further investigation, as the incidence of AI insufficiency in this population may be higher than expected.

It seems that AI is an under-recognized complication of aneurysmal SAH with significant implications for the management of cerebral vasospasm. Routine evaluation of adrenal function and basal hormonal levels may be indicated in all patients with brain injury, even in the absence of symptomatic hypopituitarism, as alterations in the hypothalamic-pituitary-adrenal axis may exacerbate the sequelae of cerebral vasospasm. However, the role of early diagnosis and potential treatment with hydrocortisone with or without fludrocortisone remains unclear. At our institution, only patients with aneurysmal SAH who demonstrate signs and symptoms of AI, particularly unresponsiveness to vasopressor therapy, are screened for hormonal pathological changes.

Ricardo J. Komotar
E. Sander Connolly, Jr.
New York, New York

A has not been commonly recognized as a complication of SAH. Of 87 patients treated for SAH over a 2-year period, the authors tested 16 patients for AI and found that indeed, two-thirds of the patients tested showed a relative AI. The primary indication for performing AI testing was SAH in patients who were “nonresponsive to vasopressor therapy.” Does this study demonstrate the incidence of AI after SAH? No, it does not. The incidence could be as high as two-thirds of all patients with SAH (by extrapolating the results from the 16 tested patients to...
The value of this study is to better define the incidence of AI in patients with SAH and to test more specifically the effects of steroid-based therapy for AI in patients with SAH to see whether primary and secondary end points such as mortality, responsiveness to vasopressor therapy, and clinical outcome are improved by treating such patients.

Bob S. Carter
Boston, Massachusetts

In this study by Weant et al. of 16 patients with aneurysmal SAH who were nonresponsive to vasopressor therapy, 69% met the criteria for relative AI. This is an important clinical finding in a neurosurgical population who are obviously at great risk from low blood pressure and cerebral perfusion pressure. Although this small retrospective series begins to address the issue of whether AI insufficiency occurs in patients with aneurysmal SAH, there are several issues that deserve comment. First, the 16 patients are a subset of 87 patients with SAH treated over the same time period. So the contention that AI occurs in 69% of patients with symptoms of AI may be true, but in the overall aneurysmal SAH population, the rate of AI may be as low as 13%. Given that testing was done only one time in symptomatic patients and over a wide time frame up to 14 days after SAH, the actual rate and time course of AI is unknown. The risk factor analysis on this small population is also difficult to interpret, given that patients were tested only one time, and it is well known that in the settings of acute traumatic brain injury and critical care in general, cortisol and adrenocorticotropic hormone levels can fluctuate widely from day to day. In future prospective analysis of this problem, daily assessments of adrenal status in all patients with SAH would be most helpful in trying to define the time course, risk factors, and clinical significance of AI in these patients.

However, as this study seems to indicate, it is likely that this hormonal derangement is quite common after SAH. Similarly, we found in our study of 80 patients with acute traumatic brain injuries that 50% of subjects met the criteria for acute AI within 10 days of injury. It is notable that in our study, the use of etomidate and metabolic suppressive agents (high-dose pentobarbital and propofol) were the strongest predictors of development of AI, which may explain why in the great majority of patients, this form of acute AI is transient. Until additional studies are completed, I agree with Weant et al. that routine testing of adrenal status should be performed in all patients with aneurysmal SAH who demonstrate possible symptoms of acute AI.

Daniel F. Kelly
Santa Monica, California

Weant et al. have provided a retrospective review of 16 patients with aneurysmal SAH who were evaluated for acute AI with cosyntropin after they were found to be unresponsive to vasopressors that were used for suboptimal blood pressures. They found that both baseline serum cortisol levels and poststimulation cortisol levels were significantly correlated with hospital stay, intensive care unit stay, and ventilator days.

Interestingly, the markers that prompted the initial evaluation for adrenal insufficiency, namely unresponsive blood pressures and increasing vasopressor requirements, showed no improvement with the administration of steroid therapy. However, one significant correlation was seen with steroid therapy, as the duration of ventilation seemed to decrease with increasing duration of steroid therapy.

This general lack of treatment benefit could signify a number of things. Certainly the size of the patient population could be inadequate for observing a difference in patients treated for relative AI. It is also conceivable that although the AI found in this patient population may have contributed to their overall medical condition, manifested as longer hospital/intensive care unit stays as well as a longer time receiving mechanical ventilation, it may have been an incidental finding unrelated to the patients’ refractory response to vasopressor therapy.

Although its retrospective nature and small study size are clear limitations, this article represents a potentially important contribution to the literature discussing the optimization of treatment for patients suffering from aneurysmal SAH. Although much of the existing literature on the matter pertains to the refractory hypotension seen in the setting of septic shock or traumatic brain injury, SAH is unique. Unlike the other conditions mentioned, vasospasm associated with SAH often mandates that the treating physician induce hypertension in a seemingly normotensive patient. Therefore, it is unclear whether the effects and subsequent treatment of relative AI would be the same if one were attempting to pharmacologically induce hypertension rather than treat severe hypotension. Nevertheless, this article provides data that may help elucidate yet another confounding variable that can occur with the treatment and management of cerebral vasospasm. Further investigation is certainly warranted.

R. Webster Crowley
Aaron S. Dumont
Charlottesville, Virginia

FUTURE MEETINGS—Congress of Neurological Surgeons

The following are the planned sites and dates for future annual meetings of the Congress of Neurological Surgeons:

<table>
<thead>
<tr>
<th>Year</th>
<th>City</th>
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<td>October 24–29</td>
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<tr>
<td>2010</td>
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<td>2012</td>
<td>Chicago, IL</td>
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<td>2013</td>
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