Pathophysiology of hyponatremia after transsphenoidal pituitary surgery

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Hyponatremia after pituitary surgery is presumed to be due to antidiuresis; however, detailed prospective investigations of water balance that would define its pathophysiology and true incidence have not been established. In this prospective study, the authors documented water balance in patients for 10 days after surgery, monitored any sodium dysregulation, further characterized the pathophysiology of hyponatremia, and correlated the degree of intraoperative stalk and posterior pituitary damage with water balance dysfunction. Ninety-two patients who underwent transsphenoidal pituitary surgery were studied. To evaluate posterior pituitary damage, a questionnaire was completed immediately after surgery in 61 patients. To examine the osmotic regulation of vasopressin secretion in normonatremic patients, water loads were administered 7 days after surgery. Patients were categorized on the basis of postoperative plasma sodium patterns.

After pituitary surgery, 25% of the patients developed spontaneous isolated hyponatremia (Day 7 ± 0.4). Twenty percent of the patients developed diabetes insipidus and 46% remained normonatremic. Plasma arginine vasopressin (AVP) was not suppressed in hyponatremic patients during hypoosmolality or in two-thirds of the normonatremic patients after water-load testing. Only one-third of the normonatremic patients excreted the water load and suppressed AVP normally. Hyponatremic patients were more natriuretic, had lower dietary sodium intake, and had similar fluid intake and cortisol and atrial natriuretic peptide (ANP) levels compared with normonatremic patients. Normonatremia, hyponatremia, and diabetes insipidus were associated with increasing degrees of surgical manipulation of the posterior lobe and pituitary stalk during surgery.

The pathophysiology of hyponatremia after transsphenoidal surgery is complex. It is initiated by pituitary damage that produces AVP secretion and dysfunctional osmoregulation in most surgically treated patients. Additional events that act together to promote the clinical expression of hyponatremia include nonatrial natriuretic peptide–related excess natriuresis, inappropriately normal fluid intake and thirst, as well as low dietary sodium intake. Patients should be monitored closely for plasma sodium, plentiful dietary sodium replacement, mild fluid restriction, and attention to symptoms of hyponatremia during the first 2 weeks after transsphenoidal surgery.

KEY WORDS • hyponatremia • pituitary tumor • thirst • natriuresis • antidiuresis

Recently we and others reported that hyponatremia is a delayed, frequent, and occasionally serious complication of transsphenoidal pituitary surgery. Lack of appropriate suppression of arginine vasopressin (AVP) secretion in a few hyponatremic hypopituitary patients and prevention of the development of hyponatremia by complete removal of the posterior pituitary in dogs suggest that hyponatremia in this setting is caused by inappropriate antidiuretic hormone release from damaged posterior pituitary terminals. However, to date, a detailed prospective study that provides a clear characterization of water balance and the role of altered regulation of AVP secretion after pituitary surgery has been lacking. The goals of this prospective study were to investigate water balance and monitor plasma (p) Na' dysregulation in patients undergoing transsphenoidal pituitary surgery and to characterize further the pathophysiology of postoperative hyponatremia. Accordingly, these three hypotheses were investigated: 1) normonatremic patients maintain normal osmotic regulation of AVP release after surgery, which prevents them from becoming hyponatremic; 2) the degree of posterior pituitary damage incurred during surgery predicts postoperative water balance; and 3) enhanced thirst and excessive fluid intake promote hyponatremia in the setting of surgically induced nonosmotic AVP release.

Clinical Material and Methods

Patient and Volunteer Populations

We prospectively studied 101 consecutive patients who underwent transsphenoidal surgery at the National Institutes of Health Clinical Center and 15 healthy volun-
teers. Each person gave written informed consent to participate in the protocol, which was approved by the Institutional Review Board of the National Institute of Child Health and Human Development.

Nine patients who had preexisting disorders of thirst and/or interfering medication (two patients), pregnancy (one patient), concurrent Na+ depletion (five patients), or preexistent diabetes insipidus (DI) (one patient) were excluded. Eighty-two adults and 10 children, all of whom had normal liver and kidney function, were included in the analysis. Diagnoses in adults included growth hormone–secreting, thyroid-stimulating hormone (TSH)–secreting, nonsecretory, and adrenocorticotropic hormone (ACTH)–secreting adenomas and craniopharyngioma. Diagnoses in children included ACTH-secreting adenomas and craniopharyngioma. The children included in this study were monitored but did not participate in the research aspects of the protocol. Fifteen healthy volunteers were examined: 10 underwent hypertonic saline tests and all 15 underwent water-load tests. Female volunteers were also studied during the follicular phase.

Characterization of Water Balance Status

Plasma Na+, (p) osmolality, and 24-hour urine osmolality collections were obtained for 10 days after surgery in all patients for the measurement of total volume, Na+ excretion, and osmolality. Blood samples were obtained every other day for measurement of AVP, oxytocin (OT), and atrial natriuretic peptide (ANP). Dietary Na+ intake was monitored before and after surgery. Fasting weights were obtained just before surgery and during the postoperative period. Fluid intake and urinary output were monitored daily.

Isolated hyponatremia was defined as a postoperative (p) Na+ level of less than 135 mmol/L lasting 2 days without preceding DI or Na+ depletion. It was classified as clinically significant and severe when the (p) Na+ level was lower than 125 mmol/L, because it is below this level that patients are symptomatic. The nadir (p) Na+ level was defined as the lowest Na+ value during the first 10 postoperative days. Depletion of Na+ was defined as a urinary Na+ level that was less than 30 mmol/L during hyponatremia. Diabetes insipidus with or without hyponatremic interphase was defined as increased (p) Na+ levels (> 145 mmol/L) or (p) osmolality (> 300 mOsm/kg H2O) in association with polyuria. A requirement for desmopressin, an AVP replacement, at discharge was defined as having persistent DI. The term “induced hyponatremia” was used to describe a (p) Na+ level that was less than 135 mmol/L after the water-load test.

Postoperative Management

Dexamethasone (0.5 mg every 6 hours) was administered intravenously in eight doses beginning immediately after surgery. In patients with Cushing’s disease, dexamethasone was withheld for 2 or 3 days (postoperative Days 2–4), without other steroid replacement, to measure morning plasma and urine cortisol levels and to determine whether biochemical remission had been achieved. All patients with Cushing’s disease thereafter continued glucocorticoid replacement with oral administration of dexamethasone 0.5 mg/day until they were discharged with a maintenance course of hydrocortisone. Headache was treated as needed during the first 48 hours with an intramuscular injection of 30 mg ketorolac tromethamine; thereafter, acetaminophen with or without codeine or propoxyphene napsylate was used. Intravenous fluids were stopped in all patients 2 to 3 days after surgery.

Management of Euvolemic Hyponatremia

Fluids were restricted in hyponatremic patients to 1200 ml/24 hours for a (p) Na+ level of 130 to 134 mmol/L, 800 ml/24 hours for a (p) Na+ level of 126 to 130 mmol/L, and 600 ml/24 hours for a (p) Na+ level of 125 mmol/L or less. Salt intake was not restricted. No patient had a plasma glucose level higher than 300 mg/dl (16.5 mmol/L) while hyponatremic. Fluids were not restricted in patients with a (p) Na+ level of 135 mmol/L or higher.

Water-Load Tests for Patients and Healthy Volunteers

To evaluate the status of osmotic regulation of AVP secretion in patients preoperatively and on postoperative Day 7 in those who remained normonatremic, a water load of 20 ml/kg of body weight was administered. The (p) Na+ and (p) osmolality, urine osmolality, and urine volume were measured hourly for 5 hours; AVP was measured before and 2 hours after water ingestion. Sixteen patients were studied before and after surgery; 13 patients were studied only before, and six only after surgery. Patients with Cushing’s disease received their morning glucocorticoid replacement (0.5 mg dexamethasone) 2 hours before the test. Patients with TSH-secreting tumors did not participate. Based on the data obtained in the 15 healthy volunteers, a normal test result was defined as a urinary excretion of more than 50% of the water ingested. Fluids were restricted until the following day in patients who excreted less than 50% of the water during the test, regardless of the Na+ level.

Hypertonic Saline Infusion Test in Healthy Volunteers

A normal range of stimulated thirst, mouth dryness, and AVP release was generated by administering 3% saline (0.512 M NaCl), at a rate of 0.1 ml/kg/birthday/minute for 90 minutes, to 10 healthy volunteers. Samples were collected every 15 minutes during the test for measurement of (p) Na+, (p) osmolality, and (p) AVP levels.

Prospective Assessment of Intraoperative Pituitary Damage

A questionnaire addressed specific details of the pituitary tumor and of the technique used to remove the adenoma. Hemihypophysectomy was performed in patients with Cushing’s disease with lateralized inferior petrosal sinus ACTH gradients in whom no tumor could be found intraoperatively. The neurosurgeon who performed the transphenoidal operations (E.H.O.) completed each questionnaire immediately after surgery.

Assessment of Thirst

Baseline thirst and mouth dryness were quantified using a visual analog scale questionnaire with a bipolar severity scale ranging from 1 to 100. Ten healthy volunteers completed this questionnaire during the water-load and
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### TABLE 1

Baseline (preoperative) characteristics and (p) Na⁺ levels in 92 patients in each of four postoperative categories of water balance

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normonatremic</th>
<th>Hyponatremic</th>
<th>DI</th>
<th>Induced Hyponatremia†</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients (total 92)</td>
<td>42</td>
<td>23</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>age (yrs)</td>
<td>38.5 ± 2.2</td>
<td>42.0 ± 3.5</td>
<td>36.0 ± 3.5</td>
<td>46.5 ± 8</td>
</tr>
<tr>
<td>sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>female (PM)</td>
<td>27 (7)</td>
<td>16 (2)</td>
<td>10 (1)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>male</td>
<td>10</td>
<td>4</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>children</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>male</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>weight (kg)</td>
<td>90.5 ± 5.0</td>
<td>68.3 ± 3.1</td>
<td>79.6 ± 6.4</td>
<td>77.5 ± 7.1</td>
</tr>
<tr>
<td>mean a.m. cortisol (normal range 7–26 µg/dl)</td>
<td>19.7 ± 1.8</td>
<td>24.5 ± 5.6</td>
<td>19.8 ± 2.1</td>
<td>22.3 ± 4.1</td>
</tr>
<tr>
<td>postop cortisol (Day 6)</td>
<td>3.6 ± 1.1</td>
<td>4.9 ± 1.9</td>
<td>1.5 ± 0.3</td>
<td>4.6 ± 2.1</td>
</tr>
<tr>
<td>triiodothyronine (normal range 75–153 ng/dl)</td>
<td>130.2 ± 13.0</td>
<td>117.2 ± 6.5</td>
<td>123.7 ± 1.3</td>
<td>117.2 ± 13.0</td>
</tr>
<tr>
<td>thyroxine (normal range 5–10 µg/dl)</td>
<td>7.0 ± 0.1</td>
<td>6.0 ± 0.1</td>
<td>7.0 ± 1.0</td>
<td>7.0 ± 1.0</td>
</tr>
<tr>
<td>type of adenoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH-secreting (68 patients)</td>
<td>29</td>
<td>18</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>TSH-secreting (6 patients)</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GH-secreting (11 patients)</td>
<td>8</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>nonsecreting (5 patients)</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>other (2 patients)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>baseline (preop) (p) Na⁺ (mmol/L)</td>
<td>140.0 ± 0.4</td>
<td>139.0 ± 0.5</td>
<td>141.0 ± 0.5</td>
<td>139.5 ± 0.6</td>
</tr>
<tr>
<td>nadir (p) Na⁺ (mmol/L) postop</td>
<td>137.0 ± 0.2‡</td>
<td>128.0 ± 0.9‡</td>
<td>136.0 ± 0.8‡</td>
<td>134.5 ± 0.5</td>
</tr>
<tr>
<td>day postop of (p) Na⁺ nadir</td>
<td>5.0 ± 0.3</td>
<td>7.0 ± 0.4</td>
<td>6.0 ± 0.3</td>
<td>7.0 ± 0.8</td>
</tr>
</tbody>
</table>

* Mean values are expressed as the mean ± SEM. Abbreviations: GH = growth hormone; PM = postmenopausal.
† Normonatremic patients made hyponatremic after water loading.
‡ p < 0.01 compared with baseline (preoperative) values.

3% NaCl tests. All patients were asked to complete a questionnaire before surgery and after surgery on postoperative Days 4 through 8 at 4 p.m. Baseline mouth dryness and thirst ratings were completed in 11 patients before surgery and in 20 patients after surgery (at the time of the [p] Na⁺ nadir).

Laboratory Tests and Assays

Blood samples were centrifuged at 4°C for 20 minutes and the serum or plasma was stored at −70°C until assayed. All steroids and peptides were measured using radioimmunoassay. Generally, all patient samples were run in the same assay to avoid interassay variability. Atrial natriuretic peptide21 and AVP (assay provided by Mitsubishi Yuka America, Inc., New York, NY)25 were measured at Hazleton Laboratories (Vienna, VA) and OTF at the University of Pittsburgh (Pittsburgh, PA). Sodium was measured using ion-selective electrodes and osmolality by the freezing-point method.

Statistical Analysis

Comparisons between four groups were made to define the water balance categories: DI (18 patients), isolated hyponatremia (23 patients), normonatremia (42 patients), and water load–induced hyponatremia (nine patients). Continuous variables were analyzed with analysis of variance and/or Student’s t-tests with Bonferroni corrections for multiple comparisons. For the surgical questionnaire data, chi-square tests were used to compare groups according to categorical factors (surgical questions). Thirst and mouth dryness numerical ratings in volunteers were compared using paired Student’s t-tests where appropriate. Thirst and mouth dryness ratings between patients before and after surgery could not be statistically compared because these data require that the same individual be studied over time. Data are presented as means ± standard error of the mean (SEM) in the text, figures, and tables; statistical results were considered to be significant at a probability level of less than 0.05.

Results

Incidence of Water Balance Disorders and Time Course of Hyponatremia

Table 1 summarizes the baseline (preoperative) characteristics and postoperative cortisol levels and details of the (p) Na⁺ nadir in all patients studied. Eighteen patients (20%) developed DI, 23 (25%) developed isolated hyponatremia, and 51 patients (55%) remained normonatremic until postoperative Day 7, when the water-load test was administered. Twenty-three adults of 51 normonatremic patients underwent postoperative water loading; nine of these developed induced hyponatremia. Thus, 42 patients remained normonatremic for the entire postoperative period (45.6%). The pattern of (p) Na⁺ levels was distinctly different in normonatremic and hyponatremic patients.
throughout the postoperative course \( (p < 0.01) \) (Fig. 1A). The time of the \( (p) \) Na\(^+\) nadir is noted in Table 1 for each group. The \( (p) \) Na\(^+\) nadir of hyponatremic patients occurred 7 days after surgery, 2 days later than the nadir of normonatremic patients (5 days after surgery). In hyponatremic patients, the \( (p) \) Na\(^+\) level remained low for several days despite fluid restriction and the slope of recovery to normonatremia resembled that of its decline (Fig. 1A). Table 1 shows that pre- and postoperative cortisol levels and thyroid hormone levels were not different between patients in each of the postoperative water balance categories.

### Isolated Hyponatremia

Three children (30%) and 20 adults (24%), 25% in all, developed spontaneous euvolume hyponatremia (Table 1). Hyponatremic events occurred postoperatively in 26% of the 68 patients with ACTH-secreting adenomas, three of six patients with TSH-secreting adenomas, and two of five patients with nonsecretory adenomas (Table 1). None of the 10 patients with acromegaly studied developed spontaneous or water load–induced hyponatremia. Seven patients (7.6%; six patients with Cushing’s disease and one with a TSH-secreting adenoma) suffered severe hyponatremia \( (p) \) Na\(^+\) \( \leq 125 \) mmol/L. The lowest level of \( (p) \) Na\(^+\) in these patients was 120 mmol/L.

Figure 1B shows the postoperative (p) AVP levels in the normonatremic and hyponatremic groups. The AVP levels were significantly higher in normonatremic patients than in hyponatremic patients \( (p < 0.05) \) on postoperative Days 2 and 4. Despite hypoosmolality, the AVP levels in the hyponatremic patients were not suppressed (the sensitivity of the assay is shown by the dashed lines in Fig. 1B) and were equivalent to those found in the normonatremic patients on postoperative Days 6 to 8. Thus, “nonosmotic” AVP secretion or leakage occurred in these patients during hyponatremia. Oxytocin levels were not different between normonatremic and hyponatremic patients (data not shown).

Fluid intake was similar in all patients studied until postoperative Days 7 through 10 (Fig. 2A). The significant decrement in fluid intake in the hyponatremic patients from postoperative Day 7 \( (p < 0.05–0.01) \) reflects the fluid restriction prescribed after expression of hyponatremia. Urine output (Fig. 2A) was decreased on postoperative Days 8 to 10 in the hyponatremic patients compared with the normonatremic patients \( (p < 0.05–0.01) \) (Fig. 2A), because of either the decreased fluid
intake and/or continued AVP secretion. Urine osmolality was higher in hyponatremic patients (Fig. 2B), which was consistent with impaired urinary dilution. We did not detect significant weight changes from baseline values in the normonatremic or the hyponatremic groups.

Baseline dietary Na\(^+\) intake before surgery was 4.1 ± 0.3 g/day. After surgery, dietary Na\(^+\) intake decreased in both groups, but it was significantly higher in normonatremic patients (3.2 ± 0.3 g/day compared with 2.3 ± 0.2 g/day in hyponatremic patients, p < 0.01). The hyponatremic group was significantly more natriuretic compared with the normonatremic group during postoperative Days 5 and 6 (Fig. 3 upper), days that preceded the mean (p) Na\(^+\) nadir in hyponatremic patients (Table 1 and Fig. 1A). Postoperatively in normonatremic patients, urinary Na\(^+\) excretion declined from Day 2 to 6 (p < 0.01 (Fig. 3 upper) and the ANP levels were significantly lower on Day 6 and 10 (p < 0.01) (Fig. 3 lower) compared with ANP levels on Day 2. Postoperatively in hyponatremic patients, ANP levels also decreased on Days 4 through 10 compared with Day 2 (p < 0.01) and were significantly lower on Day 4 compared with levels observed in normonatremic patients (p < 0.01). Thus, hyponatremic patients continue to lose Na\(^+\) in their urine despite decreased ANP levels and significantly lower dietary Na\(^+\) intake during this part of the postoperative period, changes that promote urinary Na\(^+\) conservation.

**Diabetes Insipidus**

Sixteen adults (17%) and two children (20%) developed DI (Table 1). In 11 of these 18 patients (61%) the DI persisted until discharge. The DI had a hyponatremic component in seven of the 18 patients (three were biphasic and four were triphasic responses with hyponatremia following or interfacing DI, respectively). The pattern of (p) Na\(^+\) decrements in the DI patients with a hyponatremic component of their biphasic or triphasic response paralleled the time course observed for (p) Na\(^+\) decrements in the hyponatremic patients (data not shown).

**Osmotic Regulation of AVP Release in Normonatremic Patients**

Figure 4A shows the (p) Na\(^+\) (upper), (p) osmolality (center), and urine osmolality levels (lower) observed at
baseline (Time 0) and during the subsequent 4 hours in individuals undergoing water-load testing. After water loading, the normal volunteers and the patients studied before surgery showed similar, transient decreases in (p) Na⁺ and (p) osmolality, and decreases in urinary osmolality to below 100 mOsm/kg H₂O (Fig. 4A). Figure 4B shows the percentage of total water excreted by the end of the study in all individuals studied, and the dashed line represents the percentage of water-load excretion defined as normal by our volunteer group. The mean percentage of water excreted by healthy volunteers and by patients before surgery was 109.1 mmol/L) after the test (induced hyponatremia, Table 1). Nine patients developed mild hyponatremia (130–134 mmol/L) after the test (induced hyponatremia, Table 1). However, most tumors in the hyponatremic group were microadenomas.

Table 2 shows the distribution of pituitary damage incurred during surgery according to the categories of water balance found after surgery. Only 61 (66%) of the 92 patients were studied because this surgical descriptive questionnaire was formulated after our prospective study had been initiated. Patients with DI underwent significantly more manipulation of the stalk or had incisions in the posterior lobe compared with normonatremic and hyponatremic patients. Patients with isolated hyponatremia had significantly less posterior pituitary damage and underwent less stalk traction at surgery compared with patients who developed DI. All six patients in whom a hemihypophysectomy was performed developed DI (four patients) or hyponatremia (two patients). These results indicate that the extent of surgical manipulation required to identify and remove the tumor and the posterior pituitary damage incurred at surgery are associated with the degree and type of water balance dysfunction that occurs after surgery.

There were no significant differences found between tumor size and type of water balance dysfunction when compared with the normonatremic group. However, most tumors in the hyponatremic group were microadenomas studied before surgery, and in the patients who excreted more than 50% of the water after surgery (Fig. 4C). In contrast, after surgery patients with impaired water excretion (that is, those who excreted < 50%; Fig. 4C) had no suppression or change in AVP levels after the water loading. Thus, two-thirds of normonatremic patients tested experienced dysfunction of osmotic regulation of vasopressin 1 week after transsphenoidal surgery.

### Surgical Damage to the Posterior Pituitary Gland and Water Balance Dysfunction

Table 2 shows the distribution of pituitary damage incurred during surgery according to the categories of water balance found after surgery. Only 61 (66%) of the 92 patients were studied because this surgical descriptive questionnaire was formulated after our prospective study had been initiated. Patients with DI underwent significantly more manipulation of the stalk or had incisions in the posterior lobe compared with normonatremic and hyponatremic patients. Patients with isolated hyponatremia had significantly less posterior pituitary damage and underwent less stalk traction at surgery compared with patients who developed DI. All six patients in whom a hemihypophysectomy was performed developed DI (four patients) or hyponatremia (two patients). These results indicate that the extent of surgical manipulation required to identify and remove the tumor and the posterior pituitary damage incurred at surgery are associated with the degree and type of water balance dysfunction that occurs after surgery.

There were no significant differences found between tumor size and type of water balance dysfunction when compared with the normonatremic group. However, most tumors in the hyponatremic group were microadenomas.

#### Table 2

**Surgical details in 61 patients in each postoperative category of water balance**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total No. of Patients</th>
<th>Normonatremic</th>
<th>Hyponatremic</th>
<th>Induced Hyponatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients surgical findings</td>
<td>61</td>
<td>27</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>tumor size</td>
<td>24</td>
<td>11</td>
<td>2 (TSH)§</td>
<td>7</td>
</tr>
<tr>
<td>macroadenoma</td>
<td>35</td>
<td>16</td>
<td>11 (ACTH)§</td>
<td>4</td>
</tr>
<tr>
<td>tumor not found</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>(no lateralization)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3†</td>
</tr>
<tr>
<td>tumor extended into stalk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>surgical procedure</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>hemihypophysectomy</td>
<td>6</td>
<td>0</td>
<td>2†</td>
<td>4‡</td>
</tr>
<tr>
<td>multiple incisions in gland</td>
<td>15</td>
<td>4</td>
<td>3</td>
<td>6†</td>
</tr>
<tr>
<td>pituitary stalk traction or manipulation</td>
<td>14</td>
<td>2</td>
<td>2‡</td>
<td>9‡</td>
</tr>
<tr>
<td>posterior pituitary manipulation or incisions</td>
<td>17</td>
<td>5</td>
<td>3§</td>
<td>7§</td>
</tr>
</tbody>
</table>

* Questionnaires were completed by the surgeon immediately after each surgery. Induced hyponatremia includes normonatremic patients who became hyponatremic after water loading 7 days postsurgery. Macroadenomas were at least 10 mm in diameter; microadenomas were less than 10 mm in diameter. Thirst scale: no thirst = 1, extremely thirsty = 100. Thirst scale: no thirst at all = 1, extremely thirsty = 100. Induced hyponatremia refers to patients who developed hyponatremia after water loading.

† p < 0.05 and § p < 0.01 compared with normonatremic group.

§ p < 0.05 and ¶ p < 0.01 compared with DI group.
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(11 of 14). These 11 patients developed spontaneous hyponatremia. In contrast, two patients with macroadenomas developed spontaneous hyponatremia. Four patients each in the microadenoma and macroadenoma groups underwent induced hyponatremia after water loading. Thus in this subset of patients, 25% of macroadenomas and 43% of microadenomas were associated with isolated or induced hyponatremia.

Assessment of Thirst

Thirst and mouth dryness ratings for patients and healthy volunteers are summarized in Table 3; the higher number ratings reflect higher sensations of thirst and mouth dryness. Baseline thirst ratings were different in the two groups of healthy volunteers studied for each test (before water loading and before 3% NaCl). Thirst and mouth dryness ratings in healthy volunteers were not altered after water loading. In contrast, hypertonic saline infusion elicited significant increases in (p) Na⁺ levels (from 140.5 ± 0.6 to 146 ± 0.6 mmol/L; p < 0.01), in AVP levels (from 1.2 ± 0.4 to 2.3 ± 0.6 pg/ml; p < 0.01), and in the thirst and mouth dryness ratings of the volunteers. Baseline ratings of these sensations are also shown for a small number of patients in the morning and afternoon of the day before their surgery and for patients with different categories of water balance disorder on the afternoon of the patients’ (p) Na⁺ nadir. These results obtained in healthy volunteers and in patients studied before surgery provided a relative, but not absolute, normative range. After surgery, thirst and mouth dryness ratings obtained on the day of the (p) Na⁺ nadir tended to be higher than the baseline ratings obtained in patients before surgery and in the healthy volunteers. Comparisons could not be made in the same individuals before and after surgery and, unfortunately, we do not have thirst ratings in water-loaded patients. Nonetheless, despite ambient hypoosmolality, the highest thirst ratings occurred in the hyponatremic patients.

Discussion

In this prospective study 25% of 92 patients developed isolated hyponatremia after transsphenoidal surgery, and in 7% the hyponatremia was severe with (p) Na⁺ measuring less than 125 mmol/L. The significantly higher incidence of hyponatremia in this prospective study, compared with those specified in other recent retrospective studies, likely reflects the inclusion of all hyponatremic events whether mild or severe, the fact that all of our patients remained hospitalized for a minimum of 10 days into the postoperative period, and the fact that all patients were monitored daily as part of the protocol. Our data from this study and our retrospective study, however, are in agreement with other studies that showed that hyponatremia occurs on average 7 days after surgery and with those that documented that symptomatic hyponatremia (seizure, confusion, or coma usually reported in patients who required readmission for these symptoms) is found in 2% or less of all surgically treated cases. The relatively low frequency of symptoms of hyponatremia found is likely due to the modest decrement and slow decline in Na⁺ levels after this surgery. The similar time course of development and recovery periods (Fig. 1A) suggests that a coordinated volume-regulating process of acute and chronic receptor and postreceptor events at the renal level, perhaps through changes in water channel density or sodium channels, facilitate this reliable and reversible pattern of Na⁺ dysregulation. In this regard we have recently shown that urinary aquaporin-2, the AVP-regulated water channel, may function as a marker of AVP action at the kidney, and although we were able to measure relatively low levels of aquaporin-2 in three of these patients during hyponatremia, the numbers were too few to show definitively the true renal aquaporin response in this hyponatremic setting. Hyponatremia was found with equal frequency in patients with TSH-secreting, nonsecretory, and ACTH-secreting tumors, as has been observed previously. Surprisingly, in the small subset of acromegalic patients we commonly found DI (38%) postoperatively, but no other disorder of water balance. In contrast to the findings of Kelly, et al., our results indicate a higher risk of hyponatremia in patients with microadenomas. Differences found between these studies may be due to patient population; we have larger numbers of patients with ACTH-secreting adenomas. Nonetheless, we believe that in patients with smaller tumors, with tumors that involve the pituitary stalk, or in whom the tumor cannot be found, a more complete exploration of the pituitary gland occurs than is required for larger tumors, resulting in more manipulation of and injury to the posterior lobe or the pituitary stalk. We have observed on numerous occasions upward displacement of the posterior lobe by macroadenomas, a finding usually evident on magnetic resonance imaging, a location that might "protect" the posterior lobe from the surgical field during adenoma resection. On the other hand the macroadenoma may intimately involve the stalk. Thus we believe that not just the size of the tumor but the location of the stalk/posterior lobe relative to the tumor plays a role in whether hyponatremia and/or DI occurs in patients with macroadenomas.

As suggested by other studies, this study prospectively confirms that posterior pituitary damage during surgery results in unregulated AVP release. Surprisingly this happens in most patients, both normonatremic and hyponatremic. Thus the fact that the syndrome of inappropriate antidiuretic hormone release with hyponatremia occurs spontaneously in only a subset of patients and can be induced by water loading normonatremic patients suggests that additional events must occur for clinical hyponatremia to be present.

Consistent with this possibility, we found that in the days preceding the hyponatremic nadir, hyponatremic patients have higher urinary Na⁺ loss, abnormal fluid intake, and a relatively low Na⁺ intake, all of which contribute to the development and maintenance of hyponatremia. Furthermore, because the levels of ANP were at times lower in hyponatremic patients, these findings together suggest that patients who become hyponatremic either are responding to a natriuretic stimulus other than ANP, possibly a brain natriuretic peptide, or are resistant to normally regulated antinatriuretic signals when hyponatremia ensues, perhaps as part of the complex renal escape from antidiuresis. An interesting finding in this regard is that we have not seen hyponatremia in our
acromegalic patients; one might speculate that these patients have more than sufficient levels of Na⁺ to begin with and might, therefore, be protected from excessive Na⁺ loss during the postoperative period.

Perhaps the most striking finding of this study was that two-thirds of the normonatremic patients who underwent water-load testing had dysfunctional osmotic regulation of AVP secretion and could not excrete the water normally. The fact that this abnormality was unmasked only after water-load testing tells us that clinical hyponatremia is only the “tip of the iceberg” in the disturbances of AVP secretion, thirst, and fluid intake. We suspect that in addition to Na⁺ loss and dietary deficiency, individual-specific differences in thirst and mouth dryness that govern fluid intake may diminish or enhance the likelihood of developing hyponatremia after transsphenoidal surgery. The similar fluid intakes that appeared in hyponatremic and normonatremic patients, until the hyponatremic patients had their fluids restricted (Fig. 2A), and the finding of high thirst ratings in four of our hyponatremic patients during their (p) Na⁺ nadirs (Table 3), possibly reflect such a lack of suppression of thirst and inappropriate fluid consumption in the hyponatremic patients. Osmotic suppression of drinking behavior could be either transiently defective after surgery or set at a lower threshold before the procedure. Our data did not permit differentiation between these two possibilities; however, the former explanation seems more likely because patients with pituitary tumors rarely have hyponatremia before surgery and the patients studied before surgery had similar responses to the water-load test.

Although chronic cortisol deficiency is well known to result in hyponatremia and dysregulation in AVP secretion during hypoosmolality, it is hard to evoke adrenal insufficiency as the sole causative factor in the hyponatremia in our patients because hyponatremia also occurred in patients who remained hypercortisolemic after transsphenoidal surgery, and there were no differences in the levels of cortisol (Table 1) or the level of glucocorticoid replacement between the normonatremic and hyponatremic patients with Cushing’s disease in this study or our previous study. Furthermore, others have found a similar incidence of hyponatremia postoperatively in patients with various types of tumors. These findings, combined with the results of the intraoperative assessment of posterior pituitary damage, suggest that in the immediate postoperative period the predominant mechanism of unregulated AVP secretion is through leakage from surgically damaged posterior pituitary terminals. These results have implications for the care of patients who undergo pituitary surgery. Many physicians now discharge patients 2 to 3 days after transsphenoidal surgery. Nearly 50% of these patients have a water balance disorder within 10 days of surgery, and a similar percentage of normonatremic patients have covert defects in AVP regulation. We recommend frequent (p) Na⁺ monitoring and mild fluid restriction for the first 1 to 2 weeks after surgery in patients without evidence of postoperative DI. Because these patients are natriuretic, a liberal dietary Na⁺ intake should be encouraged. Patients, physicians, and nurses should be aware that postoperative symptoms of nausea and headache may indicate clinically significant hyponatremia and that thirst may be inappropriate or enhanced while patients are in a hypoosmolar state.

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References


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