Water and Salt Metabolism Disorders Following Transsphenoidal Pituitary Surgery

Abstract

Transsphenoidal pituitary surgery is frequently complicated with mild to severe water and electrolyte disturbances in the postoperative period. These disorders are: transient diabetes insipidus, early or delayed hyponatremia, diabetes insipidus followed by hyponatremia (biphasic pattern), diabetes insipidus-hyponatremia-diabetes insipidus (triphasic pattern), permanent diabetes insipidus, and cerebral salt-wasting syndrome. Close monitoring of water intake, urine output, thirst, volume status and serum electrolytes is imperative, and a dynamic treatment plan according to the changing status of the patient is mandatory. This review will focus on the types, course and treatment of water and electrolyte disturbances observed after transsphenoidal pituitary surgery. Turk Jen 2011; 15: 28-32

Key words: Pituitary surgery, diabetes insipidus, hyponatremia, water metabolism

Introduction

In the postoperative follow-up period after transsphenoidal surgery (TSS), physicians should be alert for both neurosurgical and endocrine complications. A spectrum of water metabolism and electrolyte disturbances are among the endocrinological complications seen in the postoperative period of TSS which necessitate dynamic monitoring. The disorders of water metabolism and osmoregulation are often associated with surgery in the sellar region probably due to manipulation or vascular alterations of the neurohypophysis (1). These disorders of water and salt metabolism include transient diabetes insipidus (DI), early or delayed hyponatremia, DI followed by hyponatremia (biphasic pattern), DI-hyponatremia-DI (triphasic pattern), permanent DI, and cerebral salt-wasting syndrome (CSWS). On the other hand, these complications have been reported with different rates in several neurosurgical series possibly due to different patient characteristics, tumor types and sizes (2-5). Additionally, different definitions chosen for the diagnoses of water balance disorders and the retrospective nature of these studies also influence the rate of reported disorders (2,3,5).

In this paper, mechanism, rate, clinical presentation, and treatment of water and electrolyte disturbances observed after TSS are summarized under separate headings. Diagnoses and treatment of pre- and postoperative glucocorticoid and thyroid hormone deficiencies, which may well coexist and affect the water metabolism, are beyond the scope of this review.
Transient DI

The term transient DI denotes DI seen in the immediate postoperative period after TSS. In some series, the term isolated DI has been preferred (5). DI may occur due to disruption of the hypothalamo-pituitary stalk or trauma to the posterior pituitary gland temporarily impairing anti-diuretic hormone (ADH) secretion (6). Axonal shock from perturbations in the vascular supply to the pituitary stalk and posterior pituitary is also a suggested mechanism (1). Transient DI usually resolves as the vasopressinergic neurons regain full function (1). DI can occur at any time, but generally develops within the first 24-48 hours after surgery (1). In retrospective series, transient DI has been reported to occur in 2.3% (n=228) (8), 13.6% (n=119) (7), 18.3% (n=881) (3), 18.5% (n=319) (4) and 31% (n=1571) (2) of patients after TSS. In a prospective series involving 57 patients, transient DI was observed in 38.5% of cases (5). Risk factors for developing DI were defined as TSS for pituitary microadenoma (2,3), intraoperative cerebrospinal fluid (CSF) leak (3,7), surgery for craniopharyngioma (3), surgery for Rathke's cleft cyst (3,7), previous non-endoscopic lesion resection (7), Cushing's disease (2) and young age (2).

One of the main reasons that lies behind these different rates is the preferred definition of postsurgical DI. In their commonly-cited study which included 1571 patients, Hensen and colleagues have used the term transient polyuria instead of transient DI and used only urine output greater than 2500 ml/day as a criterion (2). In the series by Nemergut and colleagues, the diagnosis of DI was made if the patient had documented voluminous urine output (>300 ml/hour) for more than 3 hours, with a specific gravity of less than 1.005 (3). In another series, the criteria were as follows: (a) serum sodium greater than 142 mEq/L or serum osmolality greater than 300 mOsm/kg, (b) urine specific gravity less than 1.010 or urine osmolality less than 300 mOsm/kg, (c) urine output greater than 350 cc/hr for at least 2 consecutive hours or greater than 30 cc/kg/day, (d) a response to vasopressin or dDAVP treatment, as exhibited by normalization of urine output, and (e) average blood glucose less than 150 mg/dL to ensure the absence of clinically significant hyperglycemia (4). In the series by Sigounas and colleagues which included patients operated only by endoscopic TSS, criteria for the diagnosis of DI were a urine specific gravity of 1.004 or less and production of excessive volumes of urine (more than 300 ml/hour for 3 consecutive hours) in the absence of glycosuria (7). In their informative review, Ausiello and colleagues have suggested a low urine specific gravity (<1.005) combined with a high urine volume of greater than 250 cc/h for two or three consecutive hours for the diagnosis of DI. These criteria may be more rational than the previous ones due to several reasons. First, using only urine output as a criterion may be misleading as urine output changes according to the amount of the fluid administered in the postoperative period. Second, not in all patients hyponatremia will occur if the patient can compensate the fluid loss with oral water intake. Third, using hourly urine output instead of daily is a more dynamic way of evaluating the status of the patient and is valuable in the immediate postoperative period. Last but not the least, serum or urine osmolality measurement may not be possible in every center. Thus, with two practical and easy measurements, the diagnosis of transient DI is very straightforward, with these latter criteria. Patients with DI should be closely monitored for fluid intake and output, urine specific gravity and serum Na+ every 4-6 hours, thirst and volume status (1). Treatment with desmopressin, a synthetic analog of ADH acting only at V2 receptors, is required if the patient is unable to maintain adequate oral fluid intake, urine output significantly exceeds fluid intake and if hyponatremia develops (6). Due to the transient nature of the condition, desmopressin treatment should be given as needed in doses of 1-2 µg administered subcutaneously, intravenously or intramuscularly or 10µg intranasally once the nasal packing is removed (6). The patient should be allowed to drink according to thirst and should be strictly monitored to catch the resolution of transient DI. Desmopressin therapy should be held periodically to avoid over-treatment which may lead to hyponatremia (6). If the patient is to be discharged with desmopressin therapy, in case resolution occurs until the first control visit, the patient should be informed about the symptoms of hyponatremia and to take the desmopressin therapy once a week or every two weeks to pass excess urine and to be careful that polyuria is not ongoing (1). In the series by Adams and colleagues, mean resolution time was 2.9 months following TSS (4).

Hyponatremia

Hyponatremia after TSS can occur in four patterns: early hyponatremia, delayed hyponatremia, hyponatremia preceded by DI (biphasic pattern) and hyponatremia preceded and followed by DI (triphasic pattern). This section will cover only early and delayed hyponatremia.

Early hyponatremia occurring on the first postoperative day after TSS is generally not due to the transsphenoidal nature of the operation but due to the surgical intervention itself (2). In patients experiencing surgery, perioperative stress and pain are strong indirect vasovagal stimuli for ADH secretion (2). Additionally, nausea and hypotension may stimulate ADH secretion (2). Perioperative excessive hypotonic fluid infusion is another possible cause of early hyponatremia.

On the other hand, delayed hyponatremia is thought to occur due to uncontrolled release of ADH from degenerating posterior pituitary tissue or from ADH-containing neurons that have been injured during TSS (6). While some authors have preferred the term delayed hyponatremia (2,9), the term syndrome of inappropriate ADH secretion (SIADH) (1,6) and isolated hyponatremia (5) have also been used. In any case, the reason for this delayed hyponatremia may be explained by the above-mentioned mechanism, i.e. SIADH, as there are series which have demonstrated an inverse correlation between plasma ADH levels and plasma osmolality in subjects who have hyponatremia after TSS (10). Why do some patients only have an isolated hyponatremia while some develop a biphasic or triphasic pattern (see below)? In their elegant review, Loh and Verbalis have explained isolated hyponatremia with incomplete pituitary stalk injury (1). If 10-20% of the axons connecting hypothalamic neuronal cell bodies to nerve terminals in the
posterior pituitary are intact, then DI will not ensue. Nevertheless, because of the injury, uncontrolled release of ADH occurs from the degenerating nerve terminals of the posterior pituitary. After all of the ADH stored in the damaged part of the posterior pituitary gland has been released, hyponatremic phase ends. If less than 80-90% of the neuronal cell bodies in the hypothalamus have been degenerated in a retrograde fashion, DI will not follow either (1).

In general, for hyponatremia, the highest frequency occurs around the 7th day (2,4,11,12). The duration of hyponatremia varies but is typically 2-14 days (6). In the series by Hensen and colleagues, 8.4% of patients experienced hyponatremia - 2.7% in the first postoperative day, 1.7% in the third postoperative day, and 5% in the 7th postoperative day. In other series, hyponatremia was noted in 8.8% (n=319) (4), 21% (n=57) (15), 22% (n=110) (10), and 23% (n=241) (9) of patients. The incidence of symptomatic hyponatremia was 2.1% (2), 5% (9), and 16.6% (10). Risk factors for developing hyponatremia were defined as TSS for a macroadroma (10). female sex (9), transient DI (9), old age (9), patients with transient DI (9), larger tumor size (2), Cushing’s disease (2). Hyponatremia was defined as having a serum Na<135 mmol/L at any time in the postoperative period in several series (4,9,10). Adams and colleagues have identified patients with hypotonic hyponatremia with a serum sodium <135 mmol/L, a serum osmolality <280 mosm/kg, and euvoolemia in the absence of polyuria on physical exam (4). The definition criteria by Loh and Verbalis included the following: decreased effective osmolality of the extracellular fluid (plasma osmolality less than 275 mOsm/kg H2O), inappropriate urinary concentration (urine osmolality greater than 100 mOsm/kg H2O with normal renal function), clinical euvoolemia, elevated urinary sodium excretion on a normal salt and water diet, absence of other potential causes of euvolemic hypoosmolality (1). On clinical presentation, patients with serum Na+ levels >125 mmol/L are generally asymptomatic. At serum Na+ levels between 120-125 mmol/L, nausea, vomiting, anorexia, general weakness and mental alterations may appear (11). Convulsions, stupor and coma can occur at serum levels below 120 mmol/L (11). The mainstay of treatment in delayed hyponatremia is fluid restriction. As a rough guide, fluid intake <1200 ml/day for serum Na+ levels between 130-134 mmol/L, ~800 ml/day for serum levels between 126-130 mmol/L and 600 ml/day under serum levels of 125 mmol/L can be recommended (11,13). A salt-rich diet can also be commenced (2). In case clinical and biochemical signs of severe hyponatremia occur (serum Na+ <120 mmol/L), administration of 3% hypertonic saline infusion is recommended (13). The infusion rate should be calculated for each case carefully not to increase serum Na+ levels too quickly which can cause pontine and extrapontine myelolysis (13). The correction rate of hyponatremia with 3% hypertonic saline infusion should be <8-12 mmol/L/day (13,14) and stopped when serum Na+ level is 120 mmol/L or the patient is asymptomatic (13,14). The calculation of infusion rate is as follows (14):

\[
\text{Rate of Na}^+ \text{ replacement (mmol/hour) / iv. fluid strength (Na}^+ \text{ content of iv. fluid) (mmol/L) = iv. fluid infusion rate (L/hour)}
\]

**Biphasic pattern**

In the postoperative period after TSS, some patients experience DI followed by a phase of hyponatremia. This type of water metabolism disorder is called biphasic pattern. Possibly because the stalk injury and the following degeneration are not severe, a permanent DI does not ensue. A biphasic pattern has been reported in 3.4% (n=1571) (2), 3.5% (n=241) (9), 5.3% (n=319) (4), and 15.7% (n=57) (5) of patients who had TSS. If a patient who is being treated with desmopressin for DI develops hyponatremia, the clinician should be aware that this could be either due to the resolution of transient DI or development of a delayed hyponatremia due to SIADH. Under these circumstances, desmopressin treatment should be stopped and if hyponatremia persists, fluid restriction needs to be started.

**Triphasic pattern**

In the triphasic pattern, the first phase of DI usually lasts for 5-7 days, and then a second antidiuretic phase of SIADH starts (1) (Figure 1). The second phase of the triphasic response is caused by the uncontrolled release of ADH from degenerating posterior pituitary tissue, or from the remaining magnocellular neurons whose axons have been injured (1). In the first phase, the patient passes dilute urine and is polyuric, while during the second phase, the urine is concentrated and urine output decreases. Continued administration of excess water during this period can quickly lead to hyponatremia. The duration of the second phase is highly variable and can last from 2 to 14 days (1). The third phase of chronic DI develops after depletion of ADH stores from the degenerating posterior pituitary (4). In this phase, there are insufficient remaining ADH neurons capable of producing additional ADH, which results in permanent DI. Triphasic pattern was observed in 1.1% (n=1571) (2), 1.1% (n=241) (9), 2.7% (n=110) (10), and 7.1% (n=319) (4) of patients who had TSS.

**Persistent DI**

Persistent DI is a chronic complication of TSS and is a marker of severe stalk injury. It has been suggested that the level of the

![Figure 1. The three phases of triphasic pattern (adapted from Loh JA and Verbalis JG) (1)](image)
pituicy stalk section is the major determinant of permanent DI: the closer the lesion to the magnocellular cell bodies in the hypothalamus, the more likely that the hypothalamic cell bodies will degenerate, resulting in permanent DI. In a series of 24 patients receiving a low pituitary stalk section at the level of the diaphragm sella, only 62% developed permanent DI (15), compared to an incidence of 80% to 100% with higher stalk injury (16). Persistent DI was seen in 0.25% (n=157) (2), 0.6% (n=881) (3), 1.4% (17), 2% (n=241) (9), and 3.4% (n=319) (4) of patients in different series. Risk factors for permanent DI was defined as intraoperative CSF leak and having craniopharyngioma or Rathke’s cleft cyst [3].

There are case series and case reports in the literature about patients who have been operated for craniopharyngioma (18-20) and one case for macroadenoma (21) who have developed adipsic DI. In the recent case series by Crowley and colleagues, of 70 patients with craniopharyngioma (97% had undergone surgery and 42% - radiotherapy), 7.1% developed adipsic DI. On questioning, these cases reported that they never felt thirsty. These patients are particularly prone to developing hypernatreemic dehydration which increases the risk of thrombosis. Thus, in patients with adipsic DI, dose omissions in desmopressin replacement therapy may cause serious complications as they may not be able to compensate for the fluid loss with sufficient water intake.

Patients with chronic DI can be treated with oral or intranasal desmopressin. The nasal spray delivers metered single doses of 0.1 ml (10 µg). Absorbance of the spray may be diminished in patients who have a nasal discharge, mucosal atrophy, scarring or nasal congestion. The duration of action of intranasal desmopressin generally ranges from 6-12 hours, hence, twice-daily dosing is appropriate. Oral desmopressin can be preferred in subjects with mucosal scarring and chronic rhinitis. Oral tablets are available in 0.1 mg to 0.2 mg dosing options, which are much higher than the intranasal form, due to low bioavailability (99% destroyed by gastrointestinal peptidases). Patient requirements change between 200-600 µg per day to control polyuria (1).

**Cerebral salt-wasting syndrome**

CSWS is excess natriuresis and dehydration noted in subjects suffering from subarachnoid hemorrhage and brain injury, however, it is rare after pituitary tumor surgery (13). On the other hand, it should be considered as a diagnostic possibility in subjects who have hyponatremia after TSS. The mechanism how an intracranial disease causes renal salt-wasting is unclear though hypotheses involving atrial natriuretic peptide, brain natriuretic peptide/C-type peptide release, and decreased sympathetic output to the kidneys have been proposed (13). Importantly, several studies in subjects with subarachnoid hemorrhage indicate that, in addition to renal salt-wasting, there is an accompanying disordered ADH secretion (1,22). Thus, it has been suggested that in subjects with subarachnoid hemorrhage and other intracranial diseases, both conditions exist with different intensities. The treatment of CSWS includes volume replacement and maintenance of a positive sodium balance (1). Intravascular volume can be replaced with intravenous isotonic saline, and once the patient is capable of taking oral medications, NaCl tablets can be used where available (1). However, due to the possible coexistence of additional disordered ADH secretion, aggressive fluid replacement in CSWS may further aggravate hyponatremia in some of these patients. The main differential factor in CSWS and SIADH is extracellular volume status (1). Table 1 shows the diagnosis of CSWS and SIADH (23).

**Conclusions**

All patients who have undergone TSS require continuous 24-hour monitoring of fluid intake and urine output, assessment of urinary specific gravity (once or twice daily) and serum electrolyte monitoring (6). At 1 week postoperatively, serum Na+ level should be obtained. On discharge, all patients need to be informed about possible water balance disorders and to be alert regarding markedly increased or decreased urine output. The symptoms of hyponatremia, like headache, dizziness, nausea, vomiting, and altered mental status also need to be mentioned to both the patient and the family. In the postoperative period after TSS, secondary adrenal insufficiency and secondary hypothyroidism can also cause fluid retention and hyponatremia. Pituitary-adrenal axis needs be evaluated with dynamic tests, either insulin tolerance test or a 250 µg cosyntropin stimulation test according to the patient's status. In case hormonal deficiencies are detected, replacement will be started and fine tuning performed in the long-term period. As a conclusion, both the early and late postoperative follow-up of patients who have undergone TSS need to be performed by neurosurgeons and endocrinologists.

**Table 1. Diagnosis of cerebral salt-wasting syndrome (CSWS) and syndrome of inappropriate antidiuretic hormone secretion (SIADH) (1,23)**

<table>
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<tr>
<th>PARAMETER</th>
<th>CSWS</th>
<th>SIADH</th>
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<tbody>
<tr>
<td>Serum Na (mmol/L)</td>
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<td>&lt;135</td>
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<tr>
<td>Urine osmolality (mosm/kg)</td>
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<td>&lt;285</td>
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<tr>
<td>Urine Na (mmol/L)</td>
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<td>&gt;25</td>
</tr>
<tr>
<td>Weight</td>
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<td>↑</td>
</tr>
<tr>
<td>Extracellular fluid volume</td>
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<td>N, ↑</td>
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<tr>
<td>Jugular venous distention</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
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<td>↓</td>
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References


