Neurol Med Chir (Tokyo) 48, 489～494, 2008

Delayed Hyponatremia Following Transsphenoidal Surgery for Pituitary Adenoma

Jae Il LEE, Won Ho CHO*, Byung Kwan CHOI,
Seung Heon CHA, Geun Sung SONG, and Chang Hwa CHOI

The Department of Neurosurgery and
**Medical Research Institute, Pusan National University School of Medicine, Pusan, R.O.K.*

Abstract

The incidence and risk factors of symptomatic and asymptomatic hyponatremia were investigated in 94 patients who underwent transsphenoidal surgery and serum sodium level monitoring between January 2002 and December 2006. The records were retrospectively reviewed to determine the incidence and risk factors (age and sex, tumor size, endocrinologic findings) of hyponatremia. Postoperatively, the serum sodium levels of the patients were measured at least once within 2 or 3 days. Hyponatremia was found in 17 of the 94 patients, of whom 7 became symptomatic. The mean sodium level of symptomatic patients with hyponatremia at diagnosis was 123.5 mEq/l, compared with 129.8 mEq/l of asymptomatic patients. The serum sodium levels began to fall on mean postoperative day 7 and reached nadir on mean day 8. All 17 patients with hyponatremia were treated with mild fluid restriction. Four symptomatic patients with severe hyponatremia were treated with 3% hypertonic saline infusion in addition to fluid restriction. One symptomatic patient with severe hyponatremia was treated with fluid restriction only. All patients recovered within 5 days of management. Sex, tumor type, and tumor size did not correlate with development of delayed hyponatremia, but patients aged ≥50 years were more likely to develop hyponatremia. Postoperative hyponatremia after transsphenoidal surgery is more common than previously reported and may lead to fatal complications. Therefore, all patients should undergo serum electrolyte level monitoring regularly for at least 1 or 2 weeks after transsphenoidal surgery.

Key words: hyponatremia, pituitary adenoma, transsphenoidal surgery

Introduction

Disturbances of serum fluid levels and sodium balance may develop after any type of neurosurgical procedure, in particular pituitary surgery is well known to cause diabetes insipidus (DI) and hyponatremia.[1,4,7,8,10,12,14,16,17] DI usually occurs within the first few days after surgery, whereas hyponatremia tends to be delayed, even after hospital discharge, with nonspecific symptoms.[4,8,12] Therefore, hyponatremia may result in life-threatening situations, although the overall incidence and risk factors are poorly understood.

The present study examined the prevalence, time course, and predictors of delayed hyponatremia in 94 consecutive patients with pituitary adenoma who underwent transsphenoidal surgery by continuous monitoring of serum sodium levels for at least 10 days after operation.

Received January 17, 2008; Accepted July 9, 2008

Materials and Methods

Ninety-four patients, 51 males and 43 females aged 15 to 74 years (mean 42.8 years), underwent transsphenoidal resection of pituitary adenoma at our institution between January 2002 and December 2006 (Table 1). Preoperative magnetic resonance imaging showed that 85 patients had macroadenoma (≥10 mm size), and 9 patients had microadenoma. Fifty patients had endocrine inactive adenoma, 29 had prolactinoma, 11 had growth hormone (GH)-secreting adenoma, and 4 had adrenocorticotropic hormone (ACTH)-secreting adenoma. Clinical and radiological features including demographic data, tumor size, endocrinological activity, hyponatremic symptoms, and postoperative serum sodium levels were investigated.

Postoperative serum sodium levels measured every 2 or 3 days, or daily for patients with hyponatremia. Delayed hyponatremia was defined as a serum sodium level of less than 135 mEq/l on or after

Table 1 Characteristics of the patients after transsphenoidal surgery

Variable	Without delayed hyponatremia	With delayed hyponatremia	Total (%)
Total no. of patients	77	17	94
Mean patient age (yr)	42	46	42.8
Sex			
female	43	8	51 (54)
male	34	9	43 (46)
Tumor size			
microadenoma (<10 mm)	7	2	9 (10)
macroadenoma (≥10 mm)	70	15	85 (90)
Endocrine activity			
inactive	41	9	50 (53)
prolactinoma	24	5	29 (31)
GH-secreting adenoma	8	3	11 (12)
ACTH-secreting adenoma	4	0	4 (4)

ACTH: adrenocorticotropic hormone, GH: growth hormone.

Table 2 Risk stratification for symptoms in patients with hyponatremia

Degree of hyponatremia (Na, mEq/l)	Total	Symptomatic (%)	Relative risk
All (≤135)	17	7 (41)	
Mild (131–135)	8	2 (25)	1
Moderate (126–130)	4	1 (25)	1
Severe (≤125)	5	4 (80)	3.2

Table 3 Risk factors and incidence of delayed hyponatremia

Risk factor	Hyponatremia (%)	p Value
All patients	18	
Age		0.0317*
<50 yrs	13	
≥50 yrs	27	
Sex		0.4560
female	18	
male	19	
Tumor size		0.6636
microadenoma	22	
macroadenoma	18	
Tumor type		0.4313
inactive	18	
functional	18	

*Statistically significant.

postoperative day 3. Patients who developed hyponatremia up to postoperative day 2 were excluded, because such hyponatremia was attributed to intraoperative and early postoperative fluid management. We divided hyponatremia as follows: mild hyponatremia, serum sodium level 131–135 mEq/l; moderate hyponatremia, 126–130 mEq/l; and severe hyponatremia, 125 mEq/l or below.

Statistical analysis used the chi-square test with a 95% confidence interval. Statistical significance was defined as a probability value of less than 0.05.

Results

The serum sodium concentration was equal or less than 135 mEq/l after postoperative day 3 in 17 patients, 8 females and 9 males, 2 with microadenoma and 15 with macroadenoma. Nine of the 17 patients had endocrine inactive adenoma, 5 had prolactinoma, and 3 had GH-secreting adenoma.

Delayed hyponatremia was found in 17 of the 94 patients (18.1%) and symptomatic hyponatremia in 7 of 94 patients (7.4%) (Table 2). The degree of hyponatremia was mild in 8 patients, moderate in 4, and severe in 5. Risk factors for delayed hyponatremia are summarized in Table 3. There was no statistical significance between affected and unaffected patients in sex, tumor size, and endocrine activity. Patients aged ≥50 years were more likely to develop delayed hyponatremia than patients under 50 years ($p < 0.05$).

Ten patients with hyponatremia remained asymptomatic, whereas 6 patients had nausea and vomiting, and 1 patient had general weakness. Four of the seven symptomatic patients had severe, one had moderate, and two had mild hyponatremia (Table 2). Therefore, patients with severe hyponatremia were 3.2 times more likely to be symptomatic than those with mild and moderate hyponatremia. The mean sodium level at diagnosis was 123.5 mEq/l in symptomatic patients with hyponatremia, compared with 129.8 mEq/l in asymptomatic patients. The serum sodium levels began to fall on postoperative days 5 to 11 (mean day 7), and reached nadir on postoperative days 5 to 11 (mean day 8).

All 17 patients with delayed hyponatremia were treated with fluid restriction, and allowed only 500 to 1000 ml fluid intake per day. Four patients with severe hyponatremia whose sodium level did not rise above 130 mEq/l after 24 hours of fluid restriction were treated with 3% hypertonic saline infusion in addition to fluid restriction. One patient with severe hyponatremia responded to fluid restriction only. All patients recovered within 5 days of management. None of the patients manifested demyelination syndrome.

Discussion

This study showed that delayed hyponatremia after transsphenoidal surgery of pituitary adenoma is more common than previously believed. The incidence of delayed onset symptomatic hyponatremia was 2.3% in 2297 patients following transsphenoidal pituitary adenoma resection,[16] and that of delayed hyponatremia was 9% in another series.[8] The incidence of symptomatic hyponatremia was also reported at 5%.[18] In our series, the incidence of delayed hyponatremia was 18.1% and that of symptomatic hyponatremia was 7.4%. The higher incidence of hyponatremia in this study was likely due to the inclusion of all hyponatremic events, and because all patients remained hospitalized for a minimum of 7 days after surgery and serum sodium levels were observed as part of the postoperative management protocol.

In the previous large series, patients became symptomatic at 4 to 13 days after surgery (average 8 days).[16] In other reports, significant hyponatremia was not documented until at least 5 days after surgery.[4,10] Therefore, previous reports suggest that significant hyponatremia after transsphenoidal surgery does not occur until at least the latter part of the 1st postoperative week and often not until early in the 2nd week.[4,10,16] Similarly, we found that hyponatremia reached nadir on postoperative days 5 to 11 after surgery.[8,16]

Patients with delayed hyponatremia tend to be older,[8] but the present study showed age ≥ 50 years was a significant predictor for the development of delayed hyponatremia after transsphenoidal pituitary surgery. Several studies supporting influence of age as a predictive factor in delayed hyponatremia have been reported. Aging in healthy humans appears to affect the regulation of vasopressin secretion.[13] Administration of hypertonic saline to a group of young (22–48 years) and a group of old people (52–66 years) revealed that there was an increase in the sensitivity of the osmoregulatory response to vasopressin in elderly.[6] A higher incidence of hyponatremia was found in female patients.[14,18] In contrast, the present study found delayed hyponatremia with equal frequency in female and male patients.

Microadenoma and macroadenoma showed no significant difference in the development of delayed hyponatremia in this study. A higher incidence of delayed hyponatremia was found in patients who had undergone resection of macroadenoma.[8] Surgical removal is more likely to disturb the neurohypophyseal stalk and the hypothalamus, which may acutely relieve the chronic distortion of the neurohypophyseal stalk resulting in a surge of antidiuretic hormone (ADH) release, ultimately resulting in fluid overload and hyponatremia. In contrast, other reports have suggested that microadenomas may present a greater risk factor for hyponatremia because of the higher degree of the gland exploration required to identify and resect the pituitary lesion.[7,12]

Endocrine activity of the tumor had no correlation with the incidence of hyponatremia in the current study. Tumor cell type did not predict the incidence of hyponatremia, but did correlate with the severity of hyponatremia.[18] However, endocrine inactive patients had a higher risk of developing hyponatremia, and patients with Rathke cleft cysts and Cushing disease had significantly lower postoperative sodium levels than hyponatremic patients with other tumor types.[16]

Several hypotheses have been proposed for the occurrence of hyponatremia in patients who had undergone pituitary surgery. Hyponatremia occurring on postoperative days 1 to 3 is likely to result from fluid overload.[15] Although various factors such as hypothyroidism, medications, and cerebral salt wasting are all potential causes of hyponatremia in patients who have undergone pituitary surgery,[1,3,7] the most common cause of delayed postoperative hyponatremia is syndrome of inappropriate ADH (SIADH). The most likely mechanism of SIADH is release of ADH stores from manipulated neurohypophyseal cells, resulting in natriuresis and fluid retention. High serum levels of ADH are associated with the development of hyponatremia following transsphenoidal surgery of pituitary adenoma or in patients with intracranial disease.[4]

Glucocorticoid deficiency is associated with hyponatremia.[2,5] Hyponatremia may be the presenting feature of secondary adrenocortical insufficiency, even in the presence of normal basal serum cortisol concentrations.[9] This hypothesis is supported the finding that secretion of ADH may be stimulated by ACTH deficiency, and that the beneficial effect of glucocorticoid therapy is based on the suppression of ADH secretion.[11] The rapid decrease in serum cortisol concentration after removal of ACTH-producing adenoma may cause relative glucocorticoid deficiency, and predispose the patient to development of hyponatremia either by stimulating ADH secretion or by direct effects on renal tubuli.[14] The surgical procedure may also easily cause dysfunction of the posterior lobe of the gland, because of the difficulty in the localization and removal of ACTH-producing adenoma.[14] Therefore, adrenocortical insufficiency should certainly be considered in the initial evaluation of hyponatremic patients,

given that the condition is readily treatable.[8] However, limitation of present study is that the cause of hyponatremia in our patients was not clearly defined. Because we did not check the serum ADH and cortisol level during the hyponatremic period.

Anyway, delayed hyponatremia following transsphenoidal surgery was more common than previously reported in this study. Elderly patients aged ≥50 years may be more likely to develop delayed hyponatremia. Although many patients with delayed hyponatremia remain asymptomatic, they may have increased risk of severe complication. Therefore, all patients who undergo transsphenoidal surgery should have the serum sodium level monitored regularly for at least 1 or 2 weeks after the operation.

Acknowledgments

This study was supported by medical research institute grant (2007-30), Pusan National University Hospital.

References

1) Andrews BT, Fitzgerald PA, Tyrell JB, Wilson CB: Cerebral salt wasting after pituitary exploration and biopsy: case report. *Neurosurgery* 18: 469–471, 1986
2) Bethune JE, Nelson DH: Hyponatremia in hypopituitarism. *N Engl J Med* 272: 771–776, 1965
3) Coenraad MJ, Meinders AE, Taal JC, Bolk JH: Hyponatremia in intracranial disorders. *Neth J Med* 58: 123–127, 2001
4) Cusick JF, Hagen TC, Findling JW: Inappropriate secretion of antidiuretic hormone after transsphenoidal surgery for pituitary tumors. *N Engl J Med* 311: 36–38, 1984
5) Davis BB, Bloom ME, Field JB, Mintz DH: Hyponatremia in pituitary insufficiency. *Metabolism* 18: 821–832, 1969
6) Helderman JH, Vestal RE, Rowe JW, Tobin JD, Andres R, Robertson GL: The response of arginine vasopressin to intravenous ethanol and hypertonic saline in man: the impact of aging. *J Gerontol* 33: 39–47, 1978
7) Hensen J, Henig A, Fahlbusch R, Meyer M, Boehnert M, Buchfelder M: Prevalence, predictors and patterns of postoperative polyuria and hyponatremia in the immediate course after transsphenoidal surgery for pituitary adenomas. *Clin Endocrinol* (*Oxf*) 50: 431–439, 1999
8) Kelly DF, Laws ER Jr, Fossett D: Delayed hyponatremia after transsphenoidal surgery for pituitary adenoma. Report of nine cases. *J Neurosurg* 83: 363–367, 1995
9) Mansell P, Scout VL, Logan RF, Reckless JPD: Secondary adrenocortical insufficiency. *Br Med J* 307: 253–254, 1993
10) Murty GE, Lamballe P, Welch AR: Early inappropriate secretion of antidiuretic hormone after transsphenoidal pituitary adenomectomy. *J Laryngol Otol* 104: 894–895, 1990
11) Oelkers W: Hyponatremia and inappropriate secretion of vasopressin (antidiuretic hormone) in patients with hypopituitarism. *N Engl J Med* 321: 492–496, 1989
12) Olson BR, Gumowski J, Rubino D, Oldfield EH: Pathophysiology of hyponatremia after transsphenoidal pituitary surgery. *J Neurosurg* 87: 499–507, 1997
13) Rowe JW, Minaker KL, Sparrow D, Robertson GL: Age-related failure of volume-pressure-mediated vasopressin release. *J Clin Endocrinol Metab* 54: 661–664, 1982
14) Sane T, Rantakari K, Poranen A, Tahtela R, Valimaki M, Pelkonen R: Hyponatremia after transsphenoidal surgery for pituitary tumors. *J Clin Endocrinol Metab* 79: 1395–1398, 1994
15) Singer PA, Sevilla LJ: Postoperative endocrine management of pituitary tumors. *Neurosurg Clin N Am* 14: 123–138, 2003
16) Taylor SL, Tyrell JB, Wilson CB: Delayed-onset of hyponatremia after transsphenoidal surgery for pituitary adenoma. *Neurosurgery* 37: 649–654, 1995
17) Wilson CB, Dempsey LC: Transsphenoidal microsurgical removal of 250 pituitary adenomas. *J Neurosurg* 48: 13–22, 1978
18) Zada G, Liu CY, Fishback D, Singer PA, Weiss MH: Recognition and management of delayed hyponatremia following transsphenoidal pituitary surgery. *J Neurosurg* 106: 66–71, 2007

Address reprint requests to: Won Ho Cho, M.D., Department of Neurosurgery and Medical Research Institute, Pusan National University Hospital, 10, 1-Ga, Ami-Dong, Seo-Gu, Pusan, 602-739, South Korea.
e-mail: bally70@freechal.com

Commentary

How can we describe a clinically relevant, but complex symptom such as "delayed hyponatremia" after transsphenoidal operation in a shorter and more understandable way than the authors? They describe hyponatremia in 17 (18.1%) out of 94 patients, in whom pituitary adenomas were removed, which became symptomatic in 7 patients (7.4%), a higher percentage than in our experience (2.1%, see below) and in the literature. Indeed, we found even in the more complex situation of polyuria and hyponatremia, six different patterns, based on a series of 1571 patients with pituitary adenomas operated transsphenoidally and being examined by 4 neuroendo-

crine experts between 1982 and 1995.[1] The authors defined hyponatremia with values <135 mEq/l, whereas the value limit was 132 in our series.

We found altogether 8.4% of patients developing hyponatremia at some time from the first to the 10th postoperative day, presenting with symptomatic hyponatremia in 32 patients (2.1%). In more detail, 187 patients (31%) developed immediate postoperative hypotonic polyuria, 161 (10%) showed prolonged polyuria, and 37 (2.4%) had delayed hyponatremia. Biphasic (polyuria-hyponatremia) and triphasic (polyuria-hyponatremia-polyuria) patterns were seen in 53 (3.4%) and 18 (1.1%) patients, respectively, and 41 patients (2.6%) displayed immediate postoperative (day 1) hyponatremia due to fluid overload starting during surgery!

Regarding the origin of the indeed difficult pathophysiology of hyponatremia, the authors criticize themselves: "Limitations is that the cause of hyponatremia . . . was not clearly defined . . . Because we did not check serum ADH and cortisol." Although the authors found only age >50 years as a risk factor, we observed a 2.8 fold higher risk in 238 Cushing patients than in 405 acromegalic patients. The deeper reason is that, in Cushing's disease, the meticulous resection of the normal-sized gland and exploration for a microadenoma in the majority of the less then 5-mm-sized adenomas brings the surgeon closer to the posterior lobe and pituitary stalk. This phenomenon is more well known from capsule preparations and resections of Rathke's cyst and craniopharyngiomas. From this experience we speculate that the percentage of delayed hyponatremia is even higher if more intensive manipulations in the normal as well as the displaced and compressed pituitary gland are required or not.

The message from this important paper is that serum sodium has to be determined in each patient at least until the 10th postoperative day, not to overlook (delayed) hyponatremia. We agree with the treatment of mild water restriction and that 3% hypertonic solution infusion (slowly!) is only rarely indicated. Furthermore, hypocortisolism has been excluded, or adequately replaced as well. The surgeon who sends the patient "home next day," because of a successful (endoscopic?) operation, has to feel responsible for the management of a stable electrolyte water balance within the next approximately 8 to 10 days.

Antidiuretic hormone (Minirin; Ferring Pharmaceuticals, Saint-Prex, Switzerland) application, as a frequently observed "reflex attitude" in early polyuria, has to be avoided. ADH within the first 24–36 hours after surgery can induce a more severe hyponatremia, and induce a dilemma of polyuria treatment consisting of hypo- and hypernatremia, hypertonic infusions, and water restrictions, until the adequate ADH dosage is found, if this is necessary at all.

Reference

1) Hensen J, Henig A, Fahlbusch R, Meyer M, Boehnert M, Buchfelder M: Prevalence, prediction and patterns of postoperative polyuria and hyponatremia in the immediate course after transsphenoidal surgery for pituitary adenomas. Clin Endocrinol (Oxf) 50: 431–439, 1999

Rudolf FAHLBUSCH, M.D.
Center of Endocrine Neurosurgery
International Neuroscience Institute
Hannover, Germany

The authors have published the results of an analysis of 94 patients who underwent transsphenoidal surgery and serum sodium level monitoring. Although their study suffers from the usual shortcomings of a retrospective study with a small sample size, and also has one limitation in that the cause is not clearly defined due to the complexity of the etiology, this is an interesting and important manuscript showing that delayed hyponatremia occurs frequently after transsphenoidal surgery, and more often than has been previously reported. The incidence of delayed hyponatremia in their series was 18.1% and that of symptomatic hyponatremia was 7.4%. The higher incidence was likely due to the inclusion of all patients who remained hospitalized for a minimum of seven days after surgery and to the fact that serum sodium levels were observed as part of the postoperative management protocol. They also found that hyponatremia reached its nadir on postoperative days 5 to 11 after surgery. Sex, tumor type, and tumor size did not correlate with the development of delayed hyponatremia, but patients aged ≥50 years were more likely to develop hyponatremia.

I agree with the authors that measuring the serum sodium value in an outpatient basis on postoperative day 7 appears to be an effective way of identifying patients with hyponatremia and potentially preventing the onset of symptoms by allowing for early correction of hyponatremia. Patients should be advised at the time of discharge to contact their physicians if they develop symptoms such as headache, nausea, or vomiting. The physicians should also be requested to monitor serum sodium levels on an outpatient basis on postoperative day 7.

Ryoji Ishii, M.D.
Department of Neurosurgery
Kawasaki Medical School
Kurashiki, Okayama, Japan

This is a descriptive article summarizing the incidence of hyponatremia in a group of 94 patients undergoing transsphenoidal pituitary surgery. It is a relatively small group that cannot lead to significant generalizations. The group of secretory adenomas is too small, especially the ACTH secreting group, to come to any conclusions. It does point out that this entity is more common than often appreciated and I agree with that. It may be that the incidence is higher here because of their definition of hyponatremia. If it were limited to just the severe group, the incidence would be lower, but the percentage of symptomatic patients would be higher.

It would have been very beneficial if a prospective study included measurements for ADH, cortisol, and ACTH as they have been implicated in the etiology of the syndrome. We do not learn anything more about etiology from this study.

I believe that all groups of pituitary surgeons have faced this issue. My impression was that it was more frequent in ACTH secreting adenomas, but we have certainly seen it with all types and sizes of adenomas. My routine is to obtain a set of serum electrolytes one week after surgery, as an outpatient, which matches the time course seen here. I personally do not believe this is part of a triphasic form of diabetes insipidus as we do not see signs of the other phases in this group of patients. I believe it is the syndrome of inappropriate ADH secretion.

It will be enlightening to see a study that prospectively measures the correct parameters that define the etiology of this entity.

Kalmon D. Post, M.D.
Mount Sinai School of Medicine
New York, New York, U.S.A.