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ORIGINAL ARTICLE - TUMOR - OTHER

Delayed postoperative hyponatremia after endoscopic transsphenoidal surgery for pituitary adenoma

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Abstract

Background Hyponatremia generally occurs after transsphenoidal surgery (TSS) in a delayed fashion. Most patients with delayed postoperative hyponatremia (DPH) are asymptomatic or only express non-specific symptoms; consequently, DPH is associated with prolonged hospitalization. No consensus has been reached on which patients are at greatest risk of developing DPH. We reviewed patients with DPH and evaluated predictive factors for DPH.

Methods We retrospectively analyzed 107 consecutive patients who underwent endoscopic TSS for pituitary adenoma (January 2010–December 2016). Patients with DPH (hyponatremia group) and without DPH (normonatremia group) were compared according to their nadir sodium levels on postoperative days 3 to 10. We documented the patients' demographics, clinical features, and postoperative physiological characteristics.

Results Twenty-five (23.4%) patients developed DPH after endoscopic TSS. The patients' mean age was 54 ± 17 years, and 63.6% of the patients were female. The overall prevalence of DPH was 23.4%. The non-parametric $\chi 2$ test and the Mann–Whitney U test revealed statistically significant differences in age, use of antihypertensive drugs, nonfunctioning pituitary adenoma, and higher yet normal preoperative thyroid-stimulating hormone level between the hyponatremia and normonatremia groups ($P < 0.05$). Logistic regression analysis revealed that only older age was a useful independent predictive factor for DPH (odds ratio, 1.05; 95% confidence interval, 1.01–1.08; $P = 0.01$). The serum sodium levels on postoperative day 2 were significantly lower in the hyponatremia than normonatremia group ($P < 0.01$) and were negatively correlated with age ($r = -0.25$, $P < 0.05$). The cut-off age for predicting DPH was 55 years. The hospital stay was significantly longer in the hyponatremia than normonatremia group ($P < 0.01$).

Conclusions Age of more than 55 years was an independent predictive factor for DPH even after adjusting for potential confounders. Older age was negatively correlated with the serum sodium level on postoperative day 2. Preventing early decreases in the sodium level could reduce the risk of DPH.

Trial registration 1707-027

Keywords Endoscopic transsphenoidal surgery · Hyponatremia · Pituitary adenoma

This article is part of the Topical Collection on *Tumor - Other*

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Introduction

Transsphenoidal surgery (TSS) is the mainstay surgical treatment for patients with sellar and parasellar lesions, including pituitary adenoma. Endoscopic TSS has become increasingly more popular for pituitary surgery since researchers discovered that it is a safe procedure and introduced optical/electromagnetic neuronavigation and high-definition monitors [35, 41]. The complication rates associated with endoscopic TSS and microscopic TSS reportedly show no significant differences [1].

Electrolyte abnormalities such as diabetes insipidus (DI) and hyponatremia often occur during the perioperative period of TSS [14]. DI results from an antidiuretic hormone deficiency that is presumably related to surgical stress, manipulation of the neurohypophysis, or both [6, 14, 21]. Although DI has been reported to occur in 50 to 80% of patients within the first few days after surgery, it rarely becomes persistent [13, 28, 32, 36, 44]. Hyponatremia generally occurs in a more delayed fashion than transient DI, with serum sodium levels reaching their nadir on or around postoperative day (POD) 7 [10, 19, 28, 43]. Delayed postoperative hyponatremia (DPH) is usually attributed to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), cerebral salt-wasting syndrome, exogenous desmopressin administration, hypocortisolemia, or hypothyroidism [2, 3, 11, 15, 22]. However, its etiology often remains unknown because SIADH and cerebral salt-wasting syndrome (the major causes of DPH) are difficult to distinguish [27]. Although the clinical course of DPH is transient, it requires additional hospital care after TSS [7].

DPH after TSS is difficult to recognize, and its clinical course is difficult to predict. Most patients with mild DPH are asymptomatic or non-specific symptoms such as nausea and vomiting, becoming symptomatic only if the sodium level drops to 120 mEq/L [4, 26]. A serum sodium level of < 105 mEq/L is associated with a mortality rate of > 50% [5]. Therefore, symptomatic patients require hospitalization to prevent neurological complications [47]. Several clinical studies have been conducted to identify reliable predictors of DPH, but no consensus on which patients are at greatest risk of DPH has yet been reached [15, 16, 47].

We retrospectively reviewed our experience with TSS using endoscopy with a high-definition monitor and an electromagnetic neuronavigation system, focusing on the identification of predictive factors for DPH.

Materials and methods

Patients

We obtained institutional research ethics board approval (number 1707-027) for this retrospective study. We collected data from the medical charts of 107 consecutive patients who had undergone purely endoscopic TSS for treatment of pituitary adenomas from January 2010 to December 2016. The definitions of various types of pituitary adenomas were based on the clinical phenotype. After receiving informed consent from the patients, tumor samples were collected and evaluated. All surgeries were performed by three neurosurgeons specialized in endoscopic surgery.

Study design

We divided the patients into two groups according to their serum sodium concentration on PODs 3 to 10: the hyponatremia group and the normonatremia group. Hyponatremia was defined as a serum sodium level of < 135 mEq/L, as previously reported [47]. We compared demographic factors, preoperative examination findings, surgical procedures, histological examination findings, perioperative care, and postoperative examination findings between the two groups.

Magnetic resonance imaging

We used magnetic resonance imaging to evaluate the tumor size, volume, and extent of resection in all patients. Preoperative and postoperative magnetic resonance imaging scans were performed within 1 month preoperatively and within 5 days postoperatively. Tumor volume was calculated from Digital Imaging and Communications in Medicine data using iPlan Cranial planning software version 3.0 (Brainlab, Munich, Germany), as previously described [46]. The extent of tumor removal was calculated using the preoperative and postoperative tumor volumes.

Laboratory tests

The preoperative serum sodium concentration was measured within 1 week before surgery. Postoperative data were routinely collected on PODs 1 to 10 to evaluate both early and delayed hyponatremia. Once the sodium level decreased to < 135 mEq/L, its measurement was repeated every day until normalization. The levels of other electrolytes, renal function, the uric acid level, hormone levels, plasma and urine osmolality, and other urinary parameters were also assessed before and after surgery.

Surgical procedure

All patients in this study underwent transnasal endoscopic TSS for resection of a pituitary adenoma with optical or electromagnetic neuronavigation. All procedures were carried out using only an endoscopic approach, primarily with the aid of a 0°, 30°, and 70° 4-mm endoscope (Karl Storz GmbH & Co. KG, Tuttlingen, Germany) held in a UniARM (Mitaka Kohki Co., Ltd., Tokyo, Japan) set on the left side of the operator. We used the StealthStation TREON system (Medtronic, Minneapolis, MN, USA) for optical neuronavigation from 2010 to 2012 and the StealthStation S7 system (Medtronic) for electromagnetic neuronavigation from 2013 onward. The aim of the surgery was to achieve maximum decompression of the optic apparatus without injuring important structures, including the pituitary gland.

Postoperative follow-up

On the day of surgery, we managed each patient in the intensive care unit, where water balance was maintained with an intravenously administered glucose electrolyte maintenance transfusion solution. Beginning on POD 2, the patients were permitted to drink fluids. Once a patient was diagnosed with hyponatremia postoperatively, fluid restrictions were often necessary, beginning at 1500 mL/day. The limits were allowed to decrease to 1000 to 1200 mL/day depending on the patient's response, and the amount of hydrocortisone was increased accordingly.

Statistical analysis

All statistical analyses were performed using SPSS software version 21 (IBM Corp., Armonk, NY, USA). Clinical features were compared between patients with and without DPH using the non-parametric χ^2 [2] test and the Mann–Whitney U test. Stepwise logistic regression analysis was used to estimate the independent effects of predictive variables on the emergence rate of DPH. Receiver operating characteristic (ROC) analyses were used to determine the sensitivity and specificity of the clinical parameters in prediction of DPH. Data are presented as mean ± standard deviation. A P value of < 0.05 was considered to indicate statistical significance.

Results

From 2010 to 2016, a total of 107 patients with pituitary adenomas underwent endoscopic TSS. Their median age was 54 years (range, 15–82 years), and they comprised 68 females (64%) and 39 males (36%). In all cases, we performed only endoscopic surgery with a neuronavigation system, and fat grafts were placed into the sella after tumor resection. The postoperative diagnoses were nonfunctional adenoma (n = 74, 69%), growth hormone-producing adenoma (n = 23, 22%), Cushing disease (n = 5, 5%), prolactin-producing adenoma (n = 4, 4%), and thyroid-stimulating hormone (TSH)-producing adenoma (n = 1, 1%).

Among the 107 patients, 25 (23%) had developed DPH by POD 3 to 10. The serum sodium levels of these patients with DPH had remained stable up to POD 3 and then decreased to their nadir levels by POD 10. After the onset of hyponatremia, the mean length of time until normalization of the sodium concentration was 4 ± 3 days. The difference in the serum sodium levels of the two groups gradually increased with each passing day (Fig. 1a). The nadir sodium level was 128.2 ± 4.7 mEq/L in the hyponatremia group and 139.1 ± 2.2 mEq/L in the normonatremia group. Among the patients with DPH (mean age, 63 years), 48% were female (n = 12). Pathologies included endocrine-active pituitary adenomas in 3 patients (12%) and nonfunctioning adenomas in 22 patients (88%). Prior to hospital admission, none of the patients had electrolyte abnormalities, including hyponatremia. Among the 25 patients with hyponatremia, 15 (60%) were symptomatic, complaining of headache (n = 12, including postural pain), nausea and vomiting (n = 3), severe general fatigue (n = 3), and lethargy (n = 1) starting on PODs 5 to 10. The blood urea nitrogen/creatinine (BUN/Cr) ratio was not remarkably different between the preoperative and postoperative periods and was < 20 in 16 (64%) of the patients with DPH postoperatively. In addition, no patients had hypoadrenocorticism or hypothyroidism.

We then compared the hyponatremia and normonatremia groups to identify potential predictors of DPH. We found that the patients with DPH were significantly older than those without hyponatremia: the median age of the patients in the hyponatremia group was 63 years, and that in the normonatremia group was 51 years (P < 0.01). In addition, significantly more patients in the hyponatremia group had used an antihypertensive drug including an angiotensin II receptor blocker or angiotensin-converting enzyme inhibitor than those in the normonatremia group (P = 0.01). The preoperative TSH level was significantly higher in the hyponatremia than normonatremia group (P < 0.01), but the levels of other hormones, including thyroxine, were similar between the two groups (Table 1). The percentage of nonfunctioning pituitary adenomas in the hyponatremia group (88%) was significantly higher than that in the normonatremia group (63%) (P = 0.03), although only a few patients had endocrine-active pituitary adenomas in the hyponatremia group. In contrast, there were no significant differences between the two groups in other factors, including sex (P = 0.10), preoperative body weight (P = 0.54), preoperative body mass index (P = 0.47), amount of preoperative oral hydrocortisone (P = 0.38), tumor diameter or volume, operative information, amount of perioperative hydrocortisone (immediately before surgery, P = 0.53; POD 1, P = 0.43; POD 7, P = 0.43), transient DI (P = 0.36), or fluid balance on the day of surgery (P = 0.14) (Tables 1 and 2).

Next, a stepwise multiple regression analysis was performed to further test the predictors detected by the univariate analysis. Age, use of antihypertensive drugs, nonfunctioning pituitary adenoma, and higher yet normal preoperative TSH level were selected as the candidates for predictors of DPH. The stepwise procedure showed that age and the preoperative TSH level remained in the model at the parametric discriminant P value of 0.05 (Table 3). This analysis showed that older age was significantly associated with DPH (odds ratio, 1.05; 95% confidence interval, 1.01–1.08; P = 0.01) and that the preoperative TSH level tended to be associated with DPH (odds ratio, 1.39; 95% confidence interval, 1.00–1.93; P = 0.05). These results indicated that age was the most important variable consistently associated with DPH.

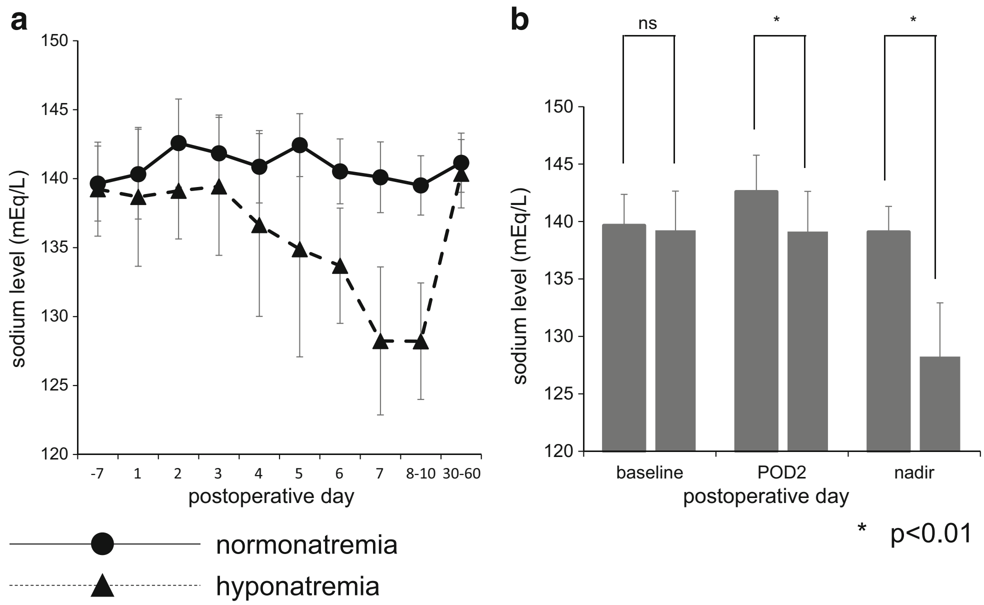

Fig. 1 **a** Changes in the serum sodium levels in the normonatremia group (serum sodium level of ≥ 135 mEq/L; black triangle, $n = 82$) and the hyponatremia group (black circle, $n = 25$) among all patients. Values are expressed as mean ± standard deviation. *$P < 0.01$ was considered statistically significant between the normonatremia and hyponatremia groups. The difference in the serum sodium levels of the two groups gradually increased with each passing day. **b** The serum sodium levels on postoperative day 2 in the 25 patients with delayed postoperative hyponatremia tended to be lower than those in the 82 patients without hyponatremia ($P < 0.01$)

To evaluate the sequential changes in the sodium level, we compared the serum sodium levels before and after surgery between the patients with and without DPH (Fig. 1a). The serum sodium levels on POD 2 were significantly lower in the 25 patients with DPH (139.1 ± 3.5 mEq/L) than in the 82 patients without hyponatremia (142.6 ± 3.2 mEq/L, $P < 0.01$). However, the baseline serum sodium levels were not significantly different between the two groups (Fig. 1b). Next, we drew a scatter plot to visualize the relationships between age and the sodium levels on POD 2 (Fig. 2) and calculated the correlation coefficient. Age was negatively associated with the sodium levels on POD 2 ($r = -0.25$, $P < 0.05$). These results suggest that older patients with DPH already had lower sodium levels on POD 2. To determine the cut-off value for predicting DPH, an ROC curve analysis was performed and showed that a cut-off age of 55 years can predict DPH (Fig. 3).

Finally, we compared the length of the postoperative hospital stay between the two groups. The patients with DPH had a 3-day longer mean hospital stay (13 days) than the patients without DPH (10 days), with a statistically significant difference ($P < 0.01$). The difference in the length of hospital stay was more significant for patients aged 55 and older than those aged 54 and under (DPH vs. normonatremia group, 13 vs. 9 days, respectively; $P < 0.01$) (Table 4).

Discussion

In this retrospective study, we examined the incidence of DPH after endoscopic TSS and attempted to identify the risk factors for hyponatremia. Postoperative hyponatremia occurred in 23.4% of patients on PODs 3 to 10. Age was significantly different between the normonatremia and hyponatremia groups, sodium levels on POD 2 were significantly different between the two groups in all cases, and age was negatively correlated with the sodium level on POD 2. The cut-off age for predicting DPH was 55 years. DPH after TSS was also associated with an increased length of hospital stay.

DPH after TSS

The prevalence of DPH after TSS for adenomas has been discussed for decades. Post-TSS hyponatremia (≤ 135 mEq/L) has been variously reported to occur in 1.8 to 35.0% of patients around POD 7 (range, POD 3–10) [20, 28, 29, 32, 34, 40, 47]. The prevalence of electrolyte disturbances after endoscopic surgery is similar to that reported after transcranial surgery [14, 31, 37, 45]. In our study, DPH occurred in 23.4% of patients, which is comparable to the incidences in the above-mentioned reports.

Etiology of DPH

The etiology of DPH has been well documented in patients with pituitary lesions. Its most common etiology is SIADH, the mechanism of which is intraoperative neuro-hypophyseal trauma that results in unregulated arginine vasopressin release [28]. Sixteen (64%) of the patients with DPH had SIADH because these patients were not dehydrated as evidenced by a BUN/Cr ratio of < 20. The TSH level was significantly

Table 1 Clinical characteristics and preoperative examination

	Total	Normonatremia	Hyponatremia	*P* value
Number of cases		82 (76%)	25 (24%)	
Background				
Age (years)	54 ± 17	51 ± 17	63 ± 12	< 0.01
Sex (f/m)	68/39	56/26	12/13	0.10
Body weight (kg)	65.2 ± 12.6	65.6 ± 12.4	63.9 ± 13.3	0.54
Body mass index	25.4 ± 4.5	25.5 ± 4.5	24.9 ± 4.2	0.47
Amount of oral hydrocortisone (mg/day)	3.0 ± 8.7	3.4 ± 9.7	1.6 ± 4.2	0.38
Number of patients taking ARB/ACEI	29	17	12	0.01
Number of recurrent cases	24	18	6	0.79
Tumor type				
Nonfunctioning adenoma	74	52 (63%)	22 (88%)	0.03
GH-producing adenoma	23	21 (26%)	2 (8%)	0.09
ACTH-producing adenoma	5	4 (5%)	1 (4%)	> 0.99
PRL-producing adenoma	4	4 (5%)	0 (0%)	0.57
TSH-producing adenoma	1	1 (1%)	0 (0%)	0.00
Preoperative laboratory test†				
Sodium (mEq/L)	139.6 ± 2.9	139.6 ± 2.7	139.2 ± 3.4	0.54
Potassium (mEq/L)	4.1 ± 0.3	4.1 ± 0.3	4.1 ± 0.3	0.67
Cl (mEq/L)	105.3 ± 3.2	105.6 ± 2.9	104.2 ± 3.8	0.06
BUN/Cr	20.7 ± 7.4	21.0 ± 7.7	19.5 ± 6.1	0.38
ACTH (pg/mL)	23.3 ± 17.8	23.9 ± 19.4	21.6 ± 10.7	0.59
TSH (μU/mL)	1.8 ± 1.5	1.6 ± 1.2	2.2 ± 1.8	< 0.01
FT4 (ng/mL)	1.2 ± 0.5	1.1 ± 0.4	1.3 ± 0.6	0.21
Cortisol (μg/dL)	10.6 ± 6.7	10.9 ± 7.3	9.4 ± 4.1	0.35
Preoperative MRI				
Anteroposterior (mm)	21.2 ± 8.4	21.2 ± 8.4	21.5 ± 8.1	0.87
Transverse (mm)	20.8 ± 7.7	20.9 ± 8.4	20.8 ± 5.6	0.98
Craniocaudal (mm)	21.9 ± 10.0	21.6 ± 10.3	22.8 ± 9.1	0.59
Tumor volume (cm^3)§	6.8 ± 7.4	7.0 ± 7.9	6.2 ± 5.5	0.63

Data are expressed as mean ± standard deviation or number. $P < 0.05$ was considered statistically significant between the normonatremia and hyponatremia groups. † Laboratory tests were performed at rest, without a loading test. § Tumor volume was calculated using iPlan Cranial planning software version 3.0 (Brainlab, Munich, Germany), as previously described [26]. *ARB*, angiotensin II receptor blocker; *ACEI*, angiotensin-converting enzyme inhibitor

higher in the hyponatremia than normonatremia group. Potential hypothyroidism did not appear, however, because the free thyroxine level was similar in the two groups. Additionally, the use of antihypertensive drugs or diuretics was significantly greater in the hyponatremia than normonatremia group. These medications, however, were unlikely to be the cause of DPH because of an adequate washout period around the time of surgery. Additionally, the water intake volume and the use of vasopressin were similar in the two groups. Hence, the etiology of DPH seems to be SIADH.

Predictive factors of DPH

Identifying reliable predictive factors of DPH is important for guiding postoperative management without the occurrence of serious complications. Although several centers have reviewed their experience, no consensus has been reached on the most important risk factors for DPH [15, 16, 47]. In the present study, age, the use of antihypertensive drugs, the nonfunctioning pituitary adenoma, and higher yet normal preoperative TSH level were related to DPH in the univariate analysis. The multivariate analysis showed that older age was the only independent predictive factor of DPH, and the ROC curve analysis detected 55 years as the cut-off age for prediction of DPH. Hussain et al. reported a relationship between older age and DPH [15]. Kinoshita et al. reported 60 years as the cut-off age for prediction of DPH [20], whereas Lee et al. reported a cut-off age of 50 years [24]. Our findings of the predictive factor and cut-off value are similar to these previous reports. The multivariate analysis also showed that

Table 2 Surgical information, perioperative management, and postoperative examination

	Total	Normonatremia	Hyponatremia	P value
Number of cases		82	25	
Operative information				
Conventional monitor + optical navigation	42	30	12	0.35
High-definition monitor + electromagnetic navigation	65	52	13	
Extent of resection (%)[†]	86.7 ± 18.9	87.4 ± 18.8	84.3 ± 19.1	0.48
Length of operation (min)	290 ± 80	293 ± 83	279 ± 68	0.44
Bleeding (mL)	133 ± 243	125 ± 201	161 ± 343	0.52
Pre/postoperative amount of hydrocortisone (mg)				
Just before surgery	93.2 ± 30.5	92.2 ± 31.8	96.6 ± 25.6	0.53
Postoperative day 0	84.6 ± 33.1	86.0 ± 30.5	80.0 ± 40.0	0.43
Postoperative day 7	15.7 ± 10.8	16.2 ± 11.7	14.2 ± 7.3	0.43
Postoperative transient diabetes insipidus	50	36	14	0.36
In-out at the day of the surgery (mL)	1214 ± 1381	1104 ± 1413	1577 ± 1203	0.14
Postoperative laboratory test				
Nadir sodium (mEq/L)	136.5 ± 5.5	139.1 ± 2.2	128.2 ± 4.7	< 0.01
Highest sodium (mEq/L)	141.5 ± 3.4	142.1 ± 2.8	139.3 ± 4.3	< 0.01
Potassium (mEq/L)	4.0 ± 0.4	4.0 ± 0.4	3.9 ± 0.4	0.45
Cl (mEq/L)	102.8 ± 4.5	104.5 ± 2.6	97.2 ± 4.9	< 0.01
BUN/Cr	19.3 ± 5.3	19.5 ± 5.6	18.3 ± 3.9	0.35
ACTH (pg/mL)	20.0 ± 11.2	19.9 ± 10.6	20.2 ± 12.8	0.93
TSH (μU/mL)	1.6 ± 1.4	1.5 ± 1.3	2.2 ± 1.8	0.04
FT4 (ng/mL)	1.3 ± 0.4	1.3 ± 0.3	1.4 ± 0.5	0.27
Cortisol (μg/dL)	12.3 ± 6.5	12.0 ± 5.9	13.0 ± 7.8	0.49

Data are expressed as mean ± standard deviation or number. $P < 0.05$ was considered statistically significant between the normonatremia and hyponatremia groups. [†] Extent of resection was calculated with preoperative and postoperative tumor volumes using iPlan Cranial planning software version 3.0 (Brainlab, Munich, Germany)

higher yet normal preoperative TSH levels were substantially related to DPH. Nagata et al. reported that the prevalence of overt hypothyroidism was significantly higher as the severity of hyponatremia progressed [26]. Pathophysiology of hyponatremia in patients with hypothyroidism is thought to induce free water retention and decrease excretion by decreasing water delivery to the diluting segment of the nephron. Our data showed that higher yet normal preoperative TSH might be related to DPH, although it needs further studies to determine the relationships between TSH and DPH after TSS.

Table 3 Logistic regression analysis of the rate of delayed hyponatremia

	Regression coefficient	OR	95% CI	P value
Age	0.04	1.05	1.01–1.08	0.01
Preoperative TSH	0.33	1.39	1.00–1.93	0.05

OR, odds ratio; *95% CI*, 95% confidence interval. $P < 0.05$ was considered statistically significant between the normonatremia and hyponatremia groups

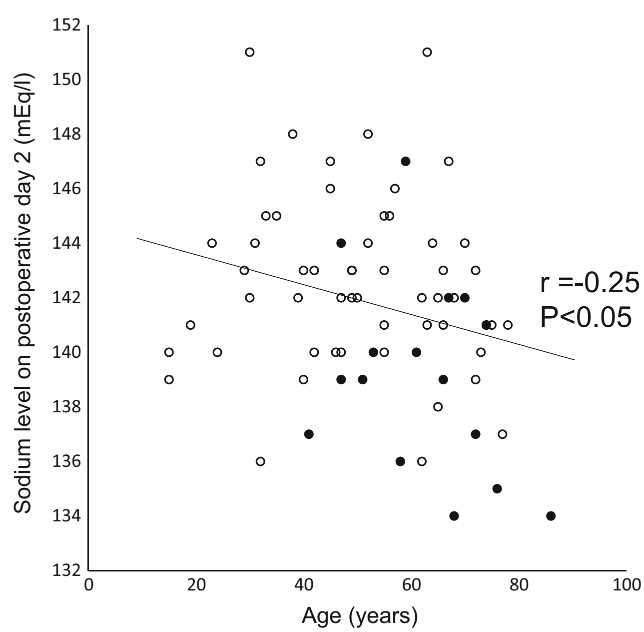

Fig. 2 Scatter plot of sodium levels on postoperative day 2 against age, with the line of equality indicated. There was a negative correlation between the age and the sodium levels on postoperative day 2 ($r = -0.25$, $P < 0.05$)

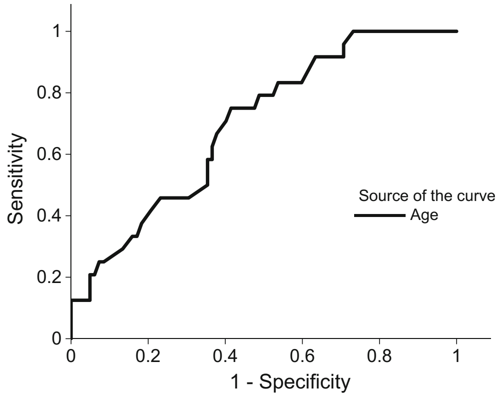

Fig. 3 Receiver operating characteristic curve analysis of age for prediction of delayed hyponatremia. An age of 55 years predicted delayed hyponatremia most exactly

Lower sodium levels at early time points after TSS

The hyponatremia group had significantly lower sodium levels than the normonatremia group as early as POD 2. This lower sodium levels that occurred on POD 2 might have been related to the DPH and caused by arginine vasopressin, which is stimulated by stress during the perioperative period or extensive neurosurgical exploration [14]. Interestingly, our data showed that the difference in the serum sodium levels between the two groups gradually increased with each passing day, which suggests the importance of sodium level management in the first few days after TSS. Takeuchi et al. reported the efficacy of moderate restriction of water intake starting on the day of surgery [38]. These reports imply that water restriction to prevent early lower sodium levels could reduce the risk of DPH, especially for patients who undergo drastic surgery.

DPH in patients of advanced age

Hyponatremia is a common electrolyte disturbance and frequently occurs in older people. The ability to maintain water and sodium balance is impaired in older persons [4, 39]. Kinoshita et al. suggested that impaired water excretion affects the serum sodium level after TSS, easily causing it to decline in older patients [20]. In the present study, older patients with DPH had lower sodium levels on POD 2. This suggests the importance of intensive care even 2 days after TSS, especially in older patients.

Endoscopic surgery and navigation

Endoscopic pituitary surgery has been widely accepted by neurosurgeons. Carrau et al. [8, 17, 18], Jho and Carrau [8, 17, 18], and Jho et al. [8, 17, 18] provided a detailed description of a purely endoscopic endonasal transsphenoidal technique. Initially, the image quality during endoscopic surgery was clearly inferior to that obtained when looking through the microscope, but the introduction of high-definition imaging makes it easy to differentiate between a tumor and the normal pituitary gland even during endoscopic surgery [35]. In the present study, no patients developed complications caused by mechanical damage (e.g., cranial nerve palsy, injury to the internal carotid artery), which reflects the safety of endoscopic surgery.

Endoscopic surgery has recently become even safer with the development of neuronavigation systems. Onizuka et al. reported a computer-assisted neurosurgical optical navigation system for TSS [30]. However, the use of optical navigation devices may be limited in transsphenoidal procedures because of interference by the surgical devices. To overcome this problem, Eboli et al. introduced the electromagnetic neuronavigation system [12]. The accuracy of electromagnetic navigation has been shown to be comparable to that of optical navigation [23]. Additionally, both the instruments and staff can move in and out of the electromagnetic field with no disruption to the surgical navigation information [33], which makes neuroendoscopic surgery more useful [23, 25, 42]. We performed endoscopic TSS with an optical navigation system until 2012, when we changed to a high-definition monitor and an electromagnetic navigation system as the supporting imaging system. The prevalence of DPH after surgery was substantially lower when using an electromagnetic navigation system than an optical navigation system. Hence, the incidence of DPH has been reduced with the development of supporting devices and after learning endoscopic procedures. We attempted to remove the tumor more aggressively with improved devices, which might not result in a

Table 4 Length of postoperative hospital stay

		Total	Normonatremia	Hyponatremia	*P* value
Length of postoperative hospital stay (days)	All the patients	11 ± 5	10 ± 5	13 ± 4	< 0.01
	The patients over 55 years	11 ± 3	9 ± 3	13 ± 4	< 0.01

Data are expressed as mean ± standard deviation. $P < 0.05$ was considered statistically significant between the normonatremia and hypon statistically significant difference in DPH between optical navigation and electromagnetic navigation.

Prolonged postoperative hospitalization

After TSS, the hyponatremia group required a longer postoperative hospital stay than the normonatremia group. Cumming et al. reported that increased age and a greater reduction in serum sodium during the inpatient stay were independently associated with an increased total length of hospital stay in patients with fragility fractures [9]. Bohl et al. retrospectively reviewed patients who underwent TSS for pituitary lesions and identified DPH as the primary cause of readmission around POD 8 [7]. In our department, all patients undergo routine care in the hospital until POD 7, resulting in the need for a longer postoperative hospital stay in patients with DPH. Hence, establishing a postoperative management protocol to prevent DPH could also prevent other serious complications and shorten the hospital stay.

Limitations

This study has several limitations. First, it was a retrospective study, and most data were acquired by chart review. Additionally, the hyponatremia was detected only during hospitalization. We therefore cannot make any conclusions regarding patients who develop DPH after discharge. Finally, these findings allow us to specifically prescribe water restriction only to those patients with lower sodium levels on POD 2 and not to all patients to prevent a nadir of hyponatremia 5 days later. Hopefully, this report will motivate other researchers to perform a multicenter prospective trial in the future.

Conclusions

We determined the incidence of DPH after endoscopic TSS. Age of more than 55 years, use of antihypertensive drugs, nonfunctioning pituitary adenoma, and higher yet normal preoperative were related to DPH in the univariate analysis. In contrast, only older age was the predictive factor for DPH in the multivariate analysis. Patients with DPH showed significantly lower sodium levels on POD 2, and older age was negatively correlated with sodium levels on POD2. Consequently, DPH after TSS was associated with an increased postoperative hospital stay. Water restriction to prevent early decreases in the sodium level could reduce the risk of DPH. Appropriate treatment should be administered whenever hyponatremia is identified.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal consent is not required.

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