Title

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Publication Date

2018-04-01

DOI

10.1016/j.jpeds.2017.11.042

Peer reviewed

HHS Public Access

Author manuscript

J Pediatr. Author manuscript; available in PMC 2019 April 01.

Published in final edited form as:

J Pediatr. 2018 April ; 195: 169–174.e1. doi:10.1016/j.jpeds.2017.11.042.

Postoperative Diabetes Insipidus and Hyponatremia in Children after Transsphenoidal Surgery for ACTH and GH Secreting Adenomas

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Abstract

Objectives—To define the incidence and risk factors of postoperative sodium alterations in pediatric patients undergoing transsphenoidal surgery (TSS) for adrenocorticotropic hormone (ACTH) and growth hormone (GH) secreting pituitary adenomas.

Study design—We retrospectively reviewed 160 patients ≤18 yr who had TSS for pituitary adenomas at our institution from 1999–2017. Variables included daily serum sodium through postoperative day 10, urine specific gravity and medications administered. We examined associations between sex, repeat surgery, manipulation of the posterior pituitary (PP), tumor invasion into the PP, tumor type and size, cerebrospinal fluid (CSF) leak, lumbar drain insertion, BMI, puberty, and development of diabetes insipidus (DI) or syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Results—Mean age was 12.9 ± 3.4y (female=81).. Patients had ACTH (150/160), and GH (10/160) producing adenomas. Forty-two (26%) patients developed DI. Among the 37/160 that required desmopressin acutely, 13/37 required it long-term. Risk of long-term need for desmopressin was significantly higher in patients who had CSF leak 9/48 ($P = .003$), lumbar drain 6/30 (p=0.019), manipulation 11/50 (p<0.001) or invasion 4/15 (p=0.022) of the PP.

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Edited by TW and WFB

The authors declare no conflicts of interest.

Portions of this study were presented at the 10th Annual Meeting of the Pediatric Endocrine Society, September 14–17, 2017, Washington, D.C.

Trial Registration ClinicalTrials.gov NCT00001595 and NCT00060541

Sixty patients developed hyponatremia, 19 due to SIADH, 39 to hypotonic fluids and 2 to cerebral salt wasting syndrome. Patients with SIADH were placed on fluid restriction; 1 received salt tablets.

Conclusions—Among 160 children that underwent TSS for pituitary adenomas, the incidence of DI and SIADH after TSS was 26% and 14%, respectively. Combined risk factors for DI and/or SIADH include female sex, manipulation of and/or tumor invasion into the PP, and CSF leak or lumbar drain.

Keywords

pituitary surgery; brain tumor; sodium abnormalities

Sodium alterations are common after transsphenoidal surgery (TSS) of the pituitary gland. Diabetes insipidus (DI), presenting as polyuria and hyperosmotic state, occurs early after pituitary surgery. The incidence of postoperative DI in adults is variable, ranging from 10 to 20% in tumors localized to the sella and even higher in larger tumors that extend to the hypothalamus.[1] Hyponatremia has also been reported after TSS and usually occurs 4–7 days postop, is transient, and has been associated with postoperative morbidity. The incidence of hyponatremia ranges from 16 to 40% in adults [2–5] and may be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) that develops from the uncontrolled release of antidiuretic hormone (ADH) by degenerating pituitary nerve terminals containing neurosecretory granules [6, 7].

The predictors and incidence of sodium alterations following TSS have been addressed in various studies in adults, however limited data exist in children. Previous studies have found variable risk factors for the development of DI or SIADH, including smaller tumor size, extensive surgical manipulation of the posterior pituitary (PP), adrenocorticotropin hormone (ACTH) producing adenoma, presence of cerebrospinal fluid (CSF) leak, low body mass index (BMI), or high estrogen levels [3, 4, 6–9]. However, results have been inconsistent and have not been studied in a large cohort children. Thus, the goal of this study was to determine the incidence and risk factors for sodium alterations in children during the first 10 days following TSS. We analyzed ACTH and GH-producing adenomas, as they are the most common functional adenomas in children where surgery is the first-line treatment[16]. The data provides guidance for patients who may be at risk and need increased surveillance.

Methods

To assess risk factors associated with the development of sodium alterations, we retrospectively reviewed clinical notes, surgical and pathology reports, medications, and laboratory results of 161 children (ages 3 – 18) who underwent sublabial open TSS at the NIH Clinical Center from 1999 to 2017.

All patients underwent surgery (161 total, 81 females), one patient was excluded because of previous permanent DI; 150 patients had ACTH producing, and 10 had growth hormone (GH) producing adenomas. All parents gave written informed consent and children gave assent to participate in the clinical trial protocol (NIH 97-CH-0076; clinicaltrials.gov:

NCT00001595) that was approved by the Institutional Review Board. Patients undergoing TSS were enrolled in a separate clinical trial (NIH 03-N-0164; clinicaltrials.gov:NCT00060541) approved by the Combined Neurosciences Institutional Review Board of the NIH. Patients were admitted before surgery, and baseline measurements included sodium, osmolality, and kidney function tests. All patients had normal renal function before surgery.

Following TSS, sodium values, fluid intake and urinary output were measured daily for 10 days. Urine specific gravity as well as serum and urine osmolality were ordered if sodium values were <135 or >145, or if there was evidence of polyuria (>4 cc/kg/h or >300 cc/h in patients weighing >75 kg).

Among patients with Cushing's disease, empiric glucocorticoid replacement was withheld during the first 5 days in order to evidence disease remission. However, if the patient developed symptoms of steroid insufficiency, dexamethasone was administered *per os* at a dose of 0.5 mg/day (adjusted for weight for patients <50kg). A maintenance dose of hydrocortisone at 12–15mg/m^2/day was prescribed for discharge in patients who had biochemical remission. In addition, during the first 12 years of the study (1999–2011) 0.5mg of IV dexamethasone were given every 6 hours starting on the day of surgery and ending at 11pm on postoperative day 1 as part of a neurosurgical clinical study that investigated the usefulness of this practice in reducing perioperative inflammation.

Diabetes insipidus was defined as polyuria and urine specific gravity <1.003 (or rapidly decreasing in the context of rising serum osmolarity). The use of desmopressin was recorded in the medication administration records. We defined "long-term need for desmopressin" as need for desmopressin after discharge.

Hyponatremia was defined as sodium <135 mmol/L. Patients were considered to have SIADH if they had euvolemic hyponatremia (with increased urine osmolality), unexplained by the administration of hypotonic fluids. Treatment for SIADH included fluid restriction to <1 L/day when sodium levels ranged between 130 and 135 mmol/L and 600–800 cc/day when sodium levels were <130 mmol/L; salt tablets were considered in patients non-responsive to fluid restriction. Cerebral salt wasting was diagnosed in patients who developed hyponatremia, per protocol were fluid restricted and despite fluid restriction continued to have polyuria, high urine osmolality, worsening hyponatremia and hypovolemia. They were treated with normal saline boluses to replete their volume loss and subsequently their sodium levels normalized without need for further interventions.

Surgical and pathology reports were reviewed to determine the size of the tumor, manipulation or invasion of the PP, and presence of CSF leak and/or spinal drain. Tumors <1 cm were classified as microadenomas, and ≥1 cm as macroadenomas. We defined manipulation of the PP present when incision or removal of PP for biopsy was reported during the surgical procedure. Pathology and intraoperative reports were reviewed to determine tumor invasion of the PP. We classified patients as having "repeat surgery" if they underwent more than one TSS (ie, 2nd or 3rd).

Sodium values were measured by ion-selective determination of analytes in mmol/L (Roche, Switzerland). Serum cortisol was collected at midnight and 8am, and measured in solid-phase using competitive chemiluminescence enzyme immunoassay (2005–2017 Siemens, Munich; <2005 Nichols Advantage, San Juan Capistrano). ACTH was measured by chemiluminiscence immunoassay (Siemens, Munich, Germany).

Statistical analyses

Data are reported as frequencies and percentages, or as mean ± standard deviation and median (inter-quartile range), as appropriate. Associations between risk factors and disease outcomes of DI, SIADH, or either DI and/or SIADH were assessed using chi-square or Fisher's exact tests, as appropriate, or Cochran-Armitage Trend test for ordered categorical variables. T-tests or Wilcoxon rank-sum tests compared continuous data between disease groups. Relative risks were computed for all risk factors, and odds ratios were computed for continuous variables using logistic regression models. A p-value less than 0.05 or a 95% Confidence Interval excluding 1.0 were considered statistically significant. Data were analyzed using SAS v.9.4 (SAS Institute Inc, Cary, North Carolina).

Results

A total of 161 patients underwent TSS. One patient was excluded due to DI after a previous pituitary surgery. Demographics are summarized in Table 1. Mean age at the time of surgery was 12.9 ± 3.4 years. Of the 81 females and 79 males, 94% (n=150) had ACTH, whereas 6% (n=10) had GH -producing adenoma. 127 patients underwent first TSS, 31 patients had a second TSS, and 2 required a third TSS for residual/recurrent tumor. Median time to the subsequent surgery was 0.9 months (IQR: 15d – 1y; range: 6d – 9y). Mean body mass index (BMI) z-score was 2.01 ± 0.75.

Forty-two (26%) patients developed DI; among these, 3 had a biphasic response with SIADH, and 2 had biphasic pattern with cerebral salt wasting (CSW). DI was seen in fewer males (n=15, 19%) than females (n=27, 33%; p=0.039) (Table II). Patients that underwent a repeat surgical intervention had higher incidence of DI than patients undergoing a first TSS: 49% vs. 21% [p=0.001; RR=2.37 (95% CI: 1.45–3.87)]. Additionally, patients that had a CSF leak or required a spinal drain had increased risk of DI when compared with no leak [44% vs. 19%, p=0.001; RR=2.29 (95% CI: 1.39–3.78)] or no drain [47% vs. 22%, p=0.006; RR=2.13 (95% CI: 1.29–3.53)], respectively. Manipulation of the PP had a strong association with the development of DI [54% vs. 14%, p<0.0001; RR=3.96 (95% CI: 2.32–6.76)]. However, no statistically significant differences were found between tumors that invaded the PP and neither the size of the adenoma nor the type of the tumor were associated with DI. No significant differences were observed in BMI z-scores or pubertal status between patients that developed DI and those that did not.

Thirty-seven (23%) patients required desmopressin during the hospitalization, among these, 13 (8% of the 160) were continued on the medication after discharge. The risk of long-term need for desmopressin was significantly increased in patients that had CSF leak versus those that did not experience a leak, had a lumbar drain versus those that did not have a drain, manipulation of the PP was noted versus no manipulation, or invasion of the PP versus no

invasion. No significant associations were found between long-term need for desmopressin and sex, repeat surgery, type of tumor, or size of adenoma (Table 2).

Hyponatremia only (without DI) was observed in 60 patients, 19 cases were attributed to SIADH, 39 to hypotonic fluids and 2 were considered part of CSW. Females were more likely to develop SIADH: 20% vs. 8% in males (p=0.026, Table 2). The incidence of SIADH was higher following the first vs. repeat surgery: 17% vs. 3%, respectively (p=0.048). Patients that developed SIADH had lower BMI z-scores than patients that did not. However, no significant associations were observed between SIADH and manipulation of the PP, type of adenoma, tumor size, presence of a lumbar drain, CSF leak, tumor invasion into the PP, or pubertal status. All patients with SIADH were placed on fluid restriction; 1 received salt tablets. Two patients had seizures resulting from hyponatremia: both patients were diagnosed with CSW syndrome and their sodium nadir levels were 117 and 127 mmol/L respectively. Among the 39 patients with fluid-induced hyponatremia, 80% (n=36) dropped their sodium levels during the first 24h post-TSS.

Sixty-one (38%) patients developed at least one of the ADH-related disturbances (DI and/or SIADH). Sodium disturbances were observed more frequently in females compared with males: 49% vs. 27% (p=0.003). Patients who had manipulation of the PP were much more likely to develop DI and/or SIADH, as were those with invasion of the tumor into the PP.

Additionally, the presence of a CSF leak as well as a spinal drain were each highly associated with development of sodium abnormalities. Having GH vs. ACTH producing adenomas and low BMI z-scores also conferred an association with sodium alterations (Table 2). No statistically significant differences were found between first and repeat surgery, tumor size, or pubertal status. The overall incidence of DI, SIADH, and mixed biphasic response in the first versus repeat surgery are depicted in Figure 1.

The day when patients developed DI was defined as the day when patients received the first dose of desmopressin or the first day of symptoms in patients that did not require desmopressin (Figure 2; available at www.jpeds.com). Among the 42 patients with DI, 88% developed it by postoperative day 2; 52% were found to have hypernatremia (n=22), of whom, 77% reached peak hypernatremia by day 1. The highest sodium peak recorded was 155 mmol/L and was seen on the day of surgery. Because the majority of patients developed DI early in the postoperative course and were promptly treated, sodium levels on day 1 post-TSS were compared between patients who developed DI and those who did not. As expected, higher sodium levels were observed in patients with DI.

Nadir sodium levels were analyzed for patients that developed SIADH. Nine (41%) patients reached nadir sodium levels in the early days post-TSS (days 1–3), and the remaining 13 reached nadir sodium late in the postoperative course (>3 days) (Figure 3; available at www.jpeds.com). All 3 patients that developed both DI and SIADH reached their nadir sodium levels day 7. Sodium values on day 1 in patients that developed SIADH were lower than in patients that did not develop SIADH.

Discussion

The incidence and risk factors for the development of sodium alterations in children following TSS are unknown. Our findings demonstrate a high incidence of sodium alterations in children following TSS, with a combined incidence of DI and SIADH of 38%. Also, these results identified various risk factors that are associated with sodium alterations. This information can be used in the clinical setting to identify high-risk patients that need closer follow-up postoperatively.

The overall incidence of DI in our study population (26%) is on the higher end of the incidence described in adults. The true incidence in children is unknown and most studies have few numbers of children. Other studies identified a higher incidence of DI after TSS in children as compared with adults [1]. However, criteria for defining DI were not uniform, and early studies found an incidence of 31% [6] using postoperative polyuria as a surrogate. More recent studies, using combined clinical criteria for DI found a lower incidence (10–20%)[3, 10–12], suggesting that preoperative fluids might have accounted for the increase in the cases of polyuria. Our rate of postoperative hyponatremia (37%) was similar to previous studies in adults (18–35%) [3, 4, 8, 13]; this was also true for the rate of SIADH (14%) [4, 7, 14].

We examined several previously described risk factors for developing post-operative sodium alterations. In our cohort, female patients had a higher risk of both SIADH and DI, which was also shown in studies in adults [4, 8, 9, 15]. Interestingly, Olson et al [8] found a lower sodium nadir in females taking estrogen replacement therapy versus female controls suggesting possible effect of sex hormones in sodium regulation. We assessed the pubertal status of our patients in order to identify differences. However, both pubertal and pre-pubertal children had similar incidence of both SIADH and DI. These results suggest that female hormones contribute to sodium regulation, but supraphysiologic doses might be needed to identify a significant difference among them. Additionally, the predominance of females in the development of both DI and SIADH opens new avenues for research in identifying hormonal, anatomical or tissue specific differences that might influence water-electrolyte homeostasis.

Consistent with previous studies, we found higher risk of DI during repeat TSS, manipulation of the PP during surgery, and presence of a CSF leak [3, 10, 12]. Anatomically it is possible that in circumstances where tumors are extensive, located superiorly in the sella, or are more difficult to find, dysregulation of the neurohypophyseal pathway can easily occur during surgery. Mixed results have been reported for the effects of the different types of adenomas on the incidence of DI [3, 5, 15]. In our cohort there were no differences between the type of adenoma and individual risk of DI or SIADH. Some studies [6, 10] suggested that ACTH-producing adenomas have a higher incidence of postoperative sodium abnormalities. However, some of them attribute it to the operative difficulty in finding the adenoma, thus leading to increased manipulation of the pituitary [6, 10]. In contrast, we found that when combining patients who developed DI and SIADH the incidence was higher in patients with GH-producing adenomas [18]. This had been mentioned by one study [3]; nonetheless, our cohort had a large proportion of patients with CD and relatively fewer with GH-producing adenomas, limiting our ability to compare the groups.

As for SIADH, studies have shown that it usually presents as delayed (>3 days postop), and the nadir sodium levels are reached around day 7 [4, 6, 8, 15]. In our cohort 60% reached nadir sodium levels > 3 days post-TSS and for the majority it occurred on day 7. Nonetheless, the remaining 40% presented early in the first 2 days post-TSS, which might mean that children have earlier dysregulation of the ADH nervous terminals, or that the abrupt decrease in hypercortisolism after surgery suppresses in a more rapid way the previously described effect of cortisol on the inhibition of ADH [17].

In contrast to DI, we found higher incidence of SIADH in the first surgery rather that the repeat surgery. We hypothesize that with further manipulation of the pituitary gland, commonly present during the repeat surgery, there is a higher risk of altering the neurohypophyseal pathways and thus lead to lack of ADH, rather than excess. In line with this, we found no differences in the incidence of SIADH and all the measures for more extensive, superiorly located and invasive tumors, which are: manipulation of the PP, presence of a leak or drain, or invasion of the tumor into the PP. We did find a significant correlation between lower BMI z-scores and SIADH; this has been previously described by Hussain et al (2013), Matsuyama et al (2014), and they suggested this might be due to impaired renal function in obesity that leads to decreased sensitivity to ADH. This might also occur because obese patients tend to have higher baseline cortisol levels and therefore leaner patients may have a higher relative cortisol deficiency in the postoperative period. It is also important to note that in our cohort the sodium disregulation caused by DI or SIADH did not lead to significant complications, in contrast to the 2 patients who were diagnosed with CSW who developed seizures from hyponatremia.

A limitation of our study was that most of our patients had ACTH-producing adenomas. Cortisol has been shown to affect water-electrolyte balance and it is difficult to determine if some patients had sodium alterations due to lack of endogenous steroids as opposed to SIADH. However, no differences were found between patients who had immediate postop steroid replacement versus the ones that had delayed replacement. We developed a risk stratifying table with the risk factors that were associated with both alterations. This might aid clinicians in identifying individuals that need closer follow-up (Table 3).

Acknowledgments

Funded by the intramural programs of the *Eunice Kennedy Shriver* National Institute of Child Health & Human Development, and the National Institute of Neurological Diseases and Stroke, National Institutes of Health, Bethesda, Maryland.

List of Abbreviations

ACTH	Adrenocorticotropin hormone
ADH	Antidiuretic hormone
BMI	Body Mass Index
CI	Confidence Interval
CSF	Cerebrospinal fluid

CSW	Cerebral Salt Wasting Syndrome
DI	Diabetes Insipidus
GH	Growth hormone
NIH	National Institutes of Health
PP	Posterior Pituitary
RR	Relative Risk
SIADH	Syndrome of Inappropriate Antidiuretic Hormone Secretion
TSS	Transsphenoidal surgery

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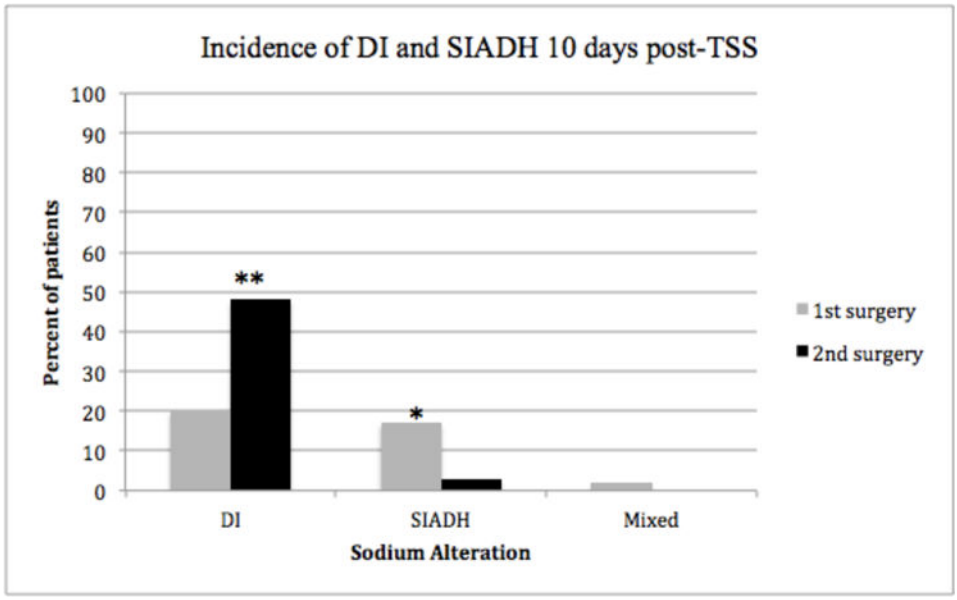

Figure 1.

Incidence of DI (n=42), SIADH (n=19), and mixed (both DI and SIADH; n=3) in pediatric patients during 10 days post-TSS, by first and second surgery.

DI: Diabetes insipidus, SIADH: Syndrome of inappropriate antidiuretic hormone secretion, TSS: transsphenoidal surgery.

**p<0.01, *p<0.05

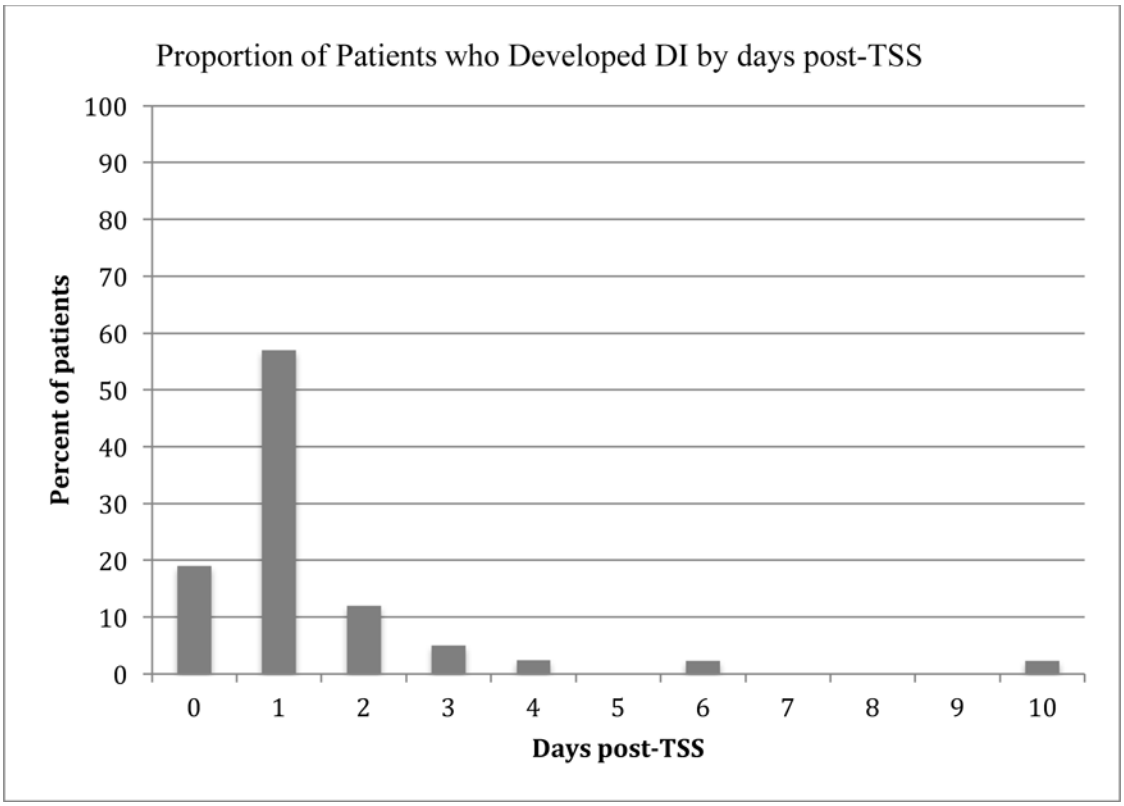

Figure 2.

Development of symptoms/first dose of desmopressin is graphed for all patients who developed DI during the 10 days post-TSS. Seventy-six percent (32/42) were diagnosed/treated by post-op day 1, 88% (37/42) by post-op day 2.

DI: Diabetes insipidus, TSS: Transsphenoidal surgery.

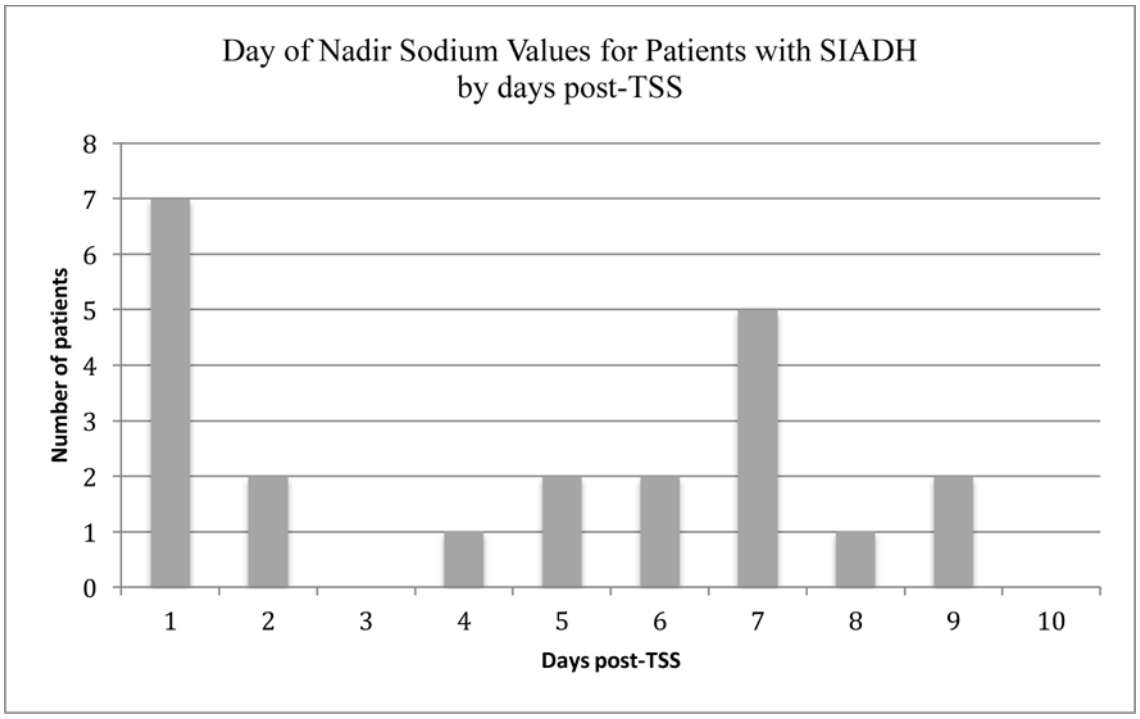

Figure 3.

Days post-TSS where nadir sodium values were reached in patients with SIADH. Nine (41%) patients had early nadir (1–2 days), and the remaining 13 patients had late nadir (>3 days).

SIADH: Syndrome of inappropriate secretion of antidiuretic hormone, TSS: transsphenoidal surgery.

Table 1

Demographics of the patients that underwent TSS.

Demographics	**Patients with TSS (n=160) n (%)**
Age, mean ± SD, y	12.9 ± 3.4
Gender (M/F)	79 (49) / 81 (51)
Race	
• Asian	8 (5)
• Black	9 (6)
• Multiracial	2 (1)
• Native Hawaiian or Other Pacific Islander	1 (<1)
• Other/unknown	25 (16)
• White	115 (72)
Ethnicity	
• Latino or Hispanic	35 (22)
• Not Latino or Hispanic	122 (76)
• Unknown	3 (2)
Type of tumor (ACTH/GH)	150 (94) / 10 (6)
Surgery (1st/repeat surgery)	127 (79) / 33 (21)
BMI z-score, mean ± SD	2.01 ± 0.75

Table 2

Incidences and RR for DI, SIADH, and either in pediatric patients 10 days post-TSS.

Risk Factor◆	DI		SIADH		DI and/or SIADH	
	n (%) (p-value)	RR (95% CI)	n (%) (p-value)	RR (95% CI)	n (%) (p-value)	RR (95% CI)
Number of patients: (n=160)	42 (26%)	—	22 (14%)	—	61 (38%)	—
Gender: M (n=79) vs. F (n=81)	15 (19%) vs. 27 (33%) (p=0.039) *	0.57 (0.33–0.99)	6 (8%) vs. 16(20%) (p=0.026) *	0.38 (0.16–0.93)	21 (27%) vs. 40 (49%) (p=0.003) **	0.54 (0.35–0.83)
Number of surgeries: Repeat (n=33) vs 1st (n=127)	16 (49%) vs. 26 (21%)(p=0.001) **	2.37 (1.45–3.87)	1 (3%) vs. 21 (17%) (p=0.048) *	0.18 (0.03–1.31)	17 (52%) vs. 44 (35%) (p=0.076)	1.49 (0.99–2.24)
Manipulation of posterior pituitary: Yes (n=50) vs. No (n=110)	27 (54%) vs. 15 (14%) (p<0.001) **	3.96 (2.32–6.76)	6 (12%) vs. 16 (15%) (p=0.665)	0.83 (0.34–1.98)	31 (62%) vs. 30 (28%) (p<0.001) **	2.27 (1.56–3.31)
Hormone excess: ACTH (n=150) vs. GH (n=10)	38 (25%) vs. 4 (40%) (p=0.292)	0.63 (0.28–1.42)	19 (13%) vs. 3 (30%) (p=0.142)	0.42 (0.15–1.19)	54 (36%) vs. 7 (70%) (p=0.044) *	0.51 (0.33–0.81)
Tumor size: Micro (n=137) vs. Macroadenoma (n=22)	35 (26%) vs. 6 (27%) (p=0.864)	0.94 (0.45–1.96)	18 (13%) vs. 4 (18%) (p=0.512)	0.72 (0.27–1.94)	50 (37%) vs. 10 (46%) (p=0.421)	0.80 (0.48–1.33)
CSF leak: Yes (n=48) vs. No (n=110)	21 (44%) vs. 21 (19%) (p=0.001) **	2.29 (1.39–3.78)	9 (19%) vs. 13 (12%) (p=0.247)	1.59 (0.73–3.46)	28 (58%) vs. 33 (30%) (p<0.001) **	1.94 (1.34–2.82)
CSF drain: Yes (n=30) vs. No (128)	14 (47%) vs. 28 (22%) (p=0.006) **	2.13 (1.29–3.53)	5 (17%) vs. 17 (13%) (p=0.572)	1.25 (0.50–3.13)	18 (60%) vs. 43 (34%) (p=0.008) **	1.79 (1.22–2.61)
Tumor invasion into posterior pituitary: Yes (n=15) vs. No (n=144)	7 (47%) vs. 35 (24%) (p=0.072)	1.92 (1.04–3.54)	3 (20%) vs. 19 (13%) (p=0.439)	1.52 (0.51–4.53)	10 (67%) vs. 51 (35%) (p=0.018) *	1.88 (1.24–2.87)
BMI Z-score:¶ Yes (for each of DI, SIADH, either) vs. No	2.01 ± 0.82 vs. 2.01 ± 0.73 (p= 0.792)	0.99 (0.62–1.58)	1.54 ± 0.69 vs. 2.09 ± 0.73 (p<0.001) **	0.42 (0.24–0.73)	1.85 ± 0.82 vs. 2.11 ± 0.69 (p=0.051)	0.630 (0.41–0.97)
Tanner stage:¶						
I (n=29)	10 (35%)	0.91	2 (7%)	2.27	12 (41%)	1.05
II (n=42)	11 (26%)	(0.71–1.17)	3 (7%)	(0.71–7.24)	13 (31%)	(0.84–1.31)
III (n=20)	5 (25%)		5 (25%)		9 (45%)	

J Pediatr. Author manuscript; available in PMC 2019 April 01.

Risk Factor◆	DI		SIADH		DI and/or SIADH	
	n (%) (p-value)	RR (95% CI)	n (%) (p-value)	RR (95% CI)	n (%) (p-value)	RR (95% CI)
IV (n=15)	1 (7%)		8 (53%)		9 (60%)	
V (n=38)	11 (29%)		4 (11%)		14 (37%)	
	(p=0.479)		(p=0.109)		(p=0.686)	
Puberty: ○ Yes (n=106) vs. No (n=38)	24 (23%) vs. 14 (37%) (p=0.088)	0.61 (0.36–1.06)	19 (18%) vs. 3 (8%) (p=0.140)	2.27 (0.71–7.24)		0.92 (0.59–1.43)

Percentages based on risk factor denominators.

◆Three patients had both DI and SIADH and were included in their respective groups

¶Odds ratio reported in place of RR

○Puberty was defined as tanner ≥ 2 in males and > 2 in females due to low estradiol levels below tanner 3 in females[19] RR=Relative Risk; CI=Confidence Interval

*p<0.05

**p<0.01

Table 3

Risk factors associated with combined DI and/or SIADH in pediatric patients during the 10-days post-TSS.

RISK FACTOR	RR (95% CI)
Female gender	1.86 (1.21–2.85)
Repeat surgery	DI: 2.37 (1.45–3.87)
Manipulation of the PP	2.27 (1.56–3.31)
Invasion of the tumor into PP	1.88 (1.23–2.87)
CSF leak	1.94 (1.34–2.82)
Spinal drain	1.79 (1.22–2.61)

CI: Confidence interval, CSF: Cerebrospinal fluid, PP: Posterior pituitary, RR: Relative Risk