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Syndrome of alternating hypernatremia and hyponatremia after hypothalamic hamartoma surgery

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Object. In this paper, the authors' goal was to describe the occurrence of alternating hypernatremia and hyponatremia in pediatric patients who underwent resection of hypothalamic hamartomas (HHs) for epilepsy. Hypernatremia in patients after pituitary or hypothalamic surgery can be caused by diabetes insipidus (DI), whereas hyponatremia can occur due to a syndrome of inappropriate antidiuretic hormone, cerebral salt wasting, or excessive administration of desmopressin (DDAVP). The triphasic response after surgery in the pituitary region can also explain variations in sodium parameters in such cases.

Methods. One hundred fifty-three patients with HH who underwent surgery were enrolled in a prospective study to monitor outcomes. Of these, 4 patients (2.6%) were noted to experience dramatic alterations in serum sodium values. The medical records of these patients were identified and evaluated.

Results. Patients' ages at surgery ranged from 1.2 to 6.0 years. All patients were girls. Two patients had Delalande Type IV lesions (of 16 total Type IV lesions surgically treated) and 2 had Type III lesions (of 39 total Type III lesions). All patients had a history of gelastic seizures refractory to medication. Seizure frequency ranged from 3 to 300 per day. After surgery, all patients experienced hypernatremia and hyponatremia. The largest fluctuation in serum sodium concentration during hospitalization in a single patient was 53 mEq/L (range 123–176 mEq/L). The mean absolute difference in maximum and minimum sodium values was 38.2 mEq/L.

All patients exhibited an initial period of immediate DI (independent of treatment) after surgery followed by a period of hyponatremia (independent of treatment), with a minimum value occurring between postoperative Days 5 and 8. All patients then returned to a hypernatremic state of DI, and 3 patients still require DDAVP for DI management. A second occurrence of hyponatremia lasting several days without DDAVP administration occurred in 2 patients during their hospitalization between periods of hypernatremia. One patient stabilized in the normal range of sodium values prior to discharge from rehabilitation without the need for further intervention. At last follow-up, 3 patients are seizure-free.

Conclusions. Severe instability of sodium homeostasis with hypernatremia and hyponatremia is seen in up to 2.6% of children undergoing open resection of HH. This risk appears to be related to HH type, with a higher risk for Types III (2 [5.1%] of 39) and IV (2 [12.5%] of 16) lesions. Here, the authors describe alternating episodes of hypernatremia and hyponatremia in the postoperative period following HH surgery. Management of this entity requires careful serial assessment of volume status and urine concentration and will often require alternating salt replacement therapy with DDAVP administration. *(DOI: 10.3171/2010.12.FOCUS10235)*

Key Words • hypothalamic hamartoma • diabetes insipidus • syndrome of inappropriate antidiuretic hormone secretion • serum sodium concentration

The relationship between postoperative hyponatremia and hypernatremia has been well described in a prospective study investigating the causes of both entities, either alone or in combination, following pituitary surgery.[12] Those authors found that, following pituitary surgery, DI was responsible for hypernatremia, and suggested that CSW rather than SIADH was responsible for hyponatremia, evidenced by hypovolemic states for both of these abnormalities (DI and CSW) that are at opposite ends of the sodium spectrum. Two other studies suggested that SIADH causes most cases of postoperative hyponatremia after transsphenoidal pituitary surgery.[14,19] Diabetes insipidus has been previously demonstrated after HH surgery.[1,3,9,10] In 1 study of patients with HH, hypernatremia (> 145 mEq/L) was found in 26 of 29

Abbreviations used in this paper: ADH = antidiuretic hormone; ANP = atrial natriuretic peptide; CSW = cerebral salt wasting; DDAVP = desmopressin; DI = diabetes insipidus; HH = hypothalamic hamartoma; SIADH = syndrome of inappropriate ADH.

patients, and 55% of these patients developed hypernatremia greater than 150 mmol/L.[3] Following surgery in the pituitary region, the sequential occurrence of CSW and SIADH has been previously demonstrated to occur in the same patient.[5,12,18] However, fluctuations in serum sodium levels resulting in sequential development of hypernatremia and hyponatremia have not been previously described following HH surgery; this entity is in line with other water electrolyte disturbances experienced after surgery in this region.

Here, we demonstrate alternating hypernatremia and hyponatremia following resection of some of the largest HHs at our center. Four patients presented here all exhibited sodium values both above and below the normal value ranges. All HHs were treated surgically and all were Delalande Type III or IV.

Methods

Since 2003, 153 patients have been treated surgically at our center for epilepsy due to HHs with 1 or more of the following approaches: transcallosal anterior interhemispheric interforniceal, orbitozygomatic, or endoscopic resection of HH. Nineteen HH lesions have been treated using Gamma Knife surgery. Patients are evaluated preoperatively by a multidisciplinary team including epileptologists, endocrinologists, and neurosurgeons for appropriate selection of treatment modality based on patients' symptoms, as well as MR imaging and video electroencephalography findings. Patients are prospectively enrolled and observed after surgery with data collection in a secure, proprietary database following informed consent under protocols approved by the institutional review board of the Barrow Neurological Institute at St. Joseph's Hospital and Medical Center. Follow-up is obtained with surveys, office visits, and telephone calls at regular intervals.

Patients are evaluated preoperatively and postoperatively for endocrinopathies including weight gain and DI by a pediatric endocrinologist (R.E.J.), seizure outcome, behavioral changes, and cognitive/developmental as well as short-term memory capacities. Four patients to date have been identified who experienced large fluctuations in their sodium values during hospitalization and for up to several months after surgery in nearly all cases.

Results

Four patients are included in this report. Data related to seizure frequency, seizure type, and seizure onset and other symptoms are shown in Table 1. None of the patients had preoperative DI, CSW, or SIADH and none were taking DDAVP before surgery. Data involving the hospital course and outcomes as they relate to seizure control, sodium levels, and other endocrinopathies are given in Table 2.

Patients' sodium values, urine specific gravities, baseline (dry) weight and nearly daily weights, and urine input and output values were monitored during their hospitalization, most of which took place in an ICU setting. The patients' laboratory values of the above-stated parameters are shown graphically in Figs. 1–4, which correspond to the patients in Cases 1–4. Desmopressin administration is also shown.

All patients immediately went into DI after surgery and required at least 1 dose of DDAVP intranasally. All patients then went into a hyponatremic state that lasted at least 4 days and persisted without DDAVP administration; that is, this occurrence was not iatrogenic. In Case 4, the hyponatremia improved and overshot the normal sodium range by Day 4, but the level returned to a hyponatremic state and hit the nadir value around Day 7 after surgery (Fig. 4). In Case 4, hyponatremia occurred several times for shorter periods later in the hospitalization, but the effect was likely iatrogenic and related to DDAVP (Fig. 4). Another patient experienced a prolonged second decrease, with a second hyponatremic state occurring between Days 14 and 18 after surgery (Fig. 2, Case 2). In this patient, as well as the patient in Case 4 and in all patients between Days 4 and 8, hyponatremia occurred independent of ongoing DDAVP administration.

Urine specific gravity, urine output, and daily weights were used in the management of sodium hemostasis (Figs. 1–4). However, weight and daily fluid output were found to be unhelpful in differentiating hyponatremia due to CSW from low sodium due to SIADH. Weights were not particularly helpful, and they were not measured consistently in our patients. All 4 patients did eventually weigh more than they did at baseline, which would indicate that their volume status at the end of hospitalization was not depleted. Volume status would be expected to be on the

TABLE 1: Preoperative characteristics: seizures and symptoms*

Case No.	Age (yrs), Sex	Age at Seizure Onset (mos)	No. of Seizures/Day	No. of AEDs at Op	Seizure Type	Symptoms
1	5.6, F	4	3–12	3	gelastic, grand mal, tonic	precocious puberty, developmental delay, rage
2	1.2, F	2	50–300	2	gelastic	precocious puberty, developmental delay†
3	6.0, F	1	5–10	3	gelastic, secondary complex partial	developmental delay, rage‡
4	3.3, F	1	8–12	2	gelastic, complex partial	precocious puberty, mild developmental delay, rage

* AEDs = antiepileptic drugs.

† As assessed postoperatively. The patient was too young preoperatively for symptom assessment.

‡ This patient exhibited mild mental retardation and short-term memory loss.

TABLE 2: Hospitalization and follow-up data related to seizure control and sodium homeostasis*

Case No.	Type (max length)	Approach	Na Value Range (mEq/L)	Symptoms From Hyponatremia (seizure or aLOC)	DDAVP Continued on Discharge	LOS (days)	FU (mos)	Seizure Outcome, Medication	Sodium Outcome	Other Endocrine Outcomes
1	IV (2.9 cm)	transcallosal	124–150	yes	no	16	2	seizure free; taking 3 AEDs	resolved before discharge from rehab	hyperthermia to 38.9°C during hospital stay
2	III (2.1 cm)	endoscopic transventricular	125–160	yes	yes	26	30	10–20 gelastic/day; taking 2 AEDs	6 mos of Na swings; Na stable on DDAVP	significant weight gain
3	III (2.1 cm)	transcallosal	123–176+†	no	yes	21	41	seizure free; taking 1 AED for mood	Na fluctuated for 3 mos; DDAVP 0.1 mg bid (last sodium value 146 mEq/L)	hyperthermia to 39.8°C during stay; increased appetite/weight gain (improving)
4	IV (3.6 cm)	transcallosal	121–160	yes	yes	27	41	seizure free; taking 1 AED	Na level hovers ~150 mEq/L; DDAVP 0.05 mg once nightly	hyperthermia during hospital stay, temperature remains slightly elevated; weight gain/aggressive behavior toward food

* aLOC = altered level of consciousness; FU = follow-up; LOS = length of stay; rehab = rehabilitation.

† This value was obtained outside the normal analytical range.

Fig. 1. Case 1. Sodium concentration **(A)** in mEq/L, urine specific gravity **(B)**, daily fluid intake *(solid line)* and daily fluid output *(dashed line)* in ml **(C)**, and weight in kg **(D)**. The values on the x axes indicate the postoperative days. The *asterisk* in panel **A** represents the time of administration of DDAVP. Time zero for sodium concentration represents baseline sodium level. Time zero for weight represents baseline dry weight.

dehydration end of the spectrum had patients experienced both DI (which they did) and CSW (characterized by a low volume state) without periods of SIADH. This was not the case; SIADH was more likely occurring. In most of the patients, except the one in Case 4, fluid intake and urine output were closely matched. In Case 4, although demonstrating fluid output greater than fluid input for the majority of the stay, the patient managed to gain weight. This raises the concern or limitation that fluid and weight measurements in the ICU are not always completely accurate or reliable in predicting volume status.

Most patients exhibited long-term impairments in the ability to regulate water and electrolytes, continued to have central DI, and remained on DDAVP at last follow-up. One patient had resolution of the fluctuating sodium prior to discharge and did not require DDAVP postoperatively (Case 1). There were also several other associated endocrine disturbances including hyperphagia and hyperthermia (Table 2). Three of the 4 patients with these sodium perturbations experienced permanent injury and continued to have DI. Three of the patients had undergone transcallosal surgery, and at surgery, a very aggressive resection was obtained in all 3, with the percentages of resection based on volumetric calculations totaling 92%,

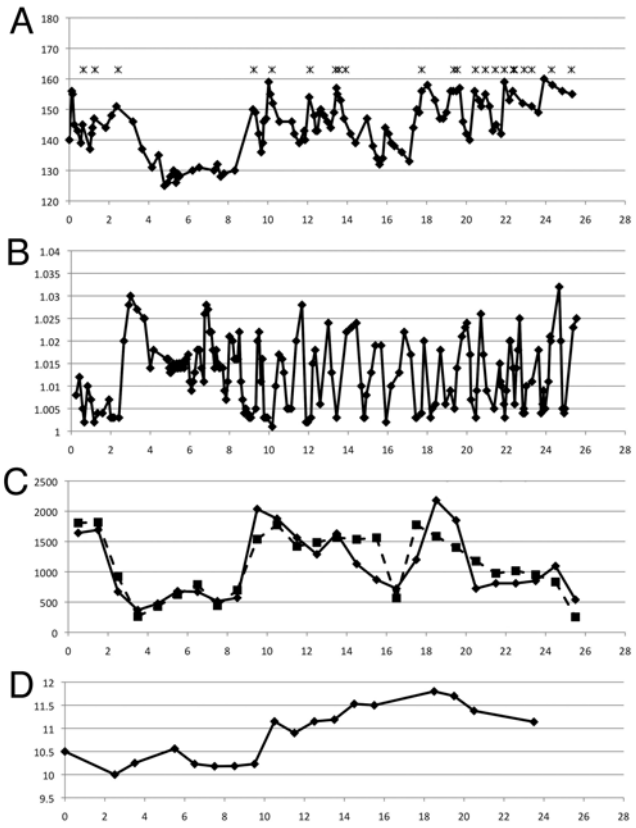

Fig. 2. Case 2. Sodium concentration **(A)** in mEq/L, urine specific gravity **(B)**, daily fluid intake *(solid line)* and daily fluid output *(dashed line)* in ml **(C)**, and weight in kg **(D)**. The values on the x axes indicate the postoperative days. *Asterisks* in panel **A** represent the time of administration of DDAVP. Time zero for sodium concentration represents baseline sodium level. Time zero for weight represents baseline dry weight.

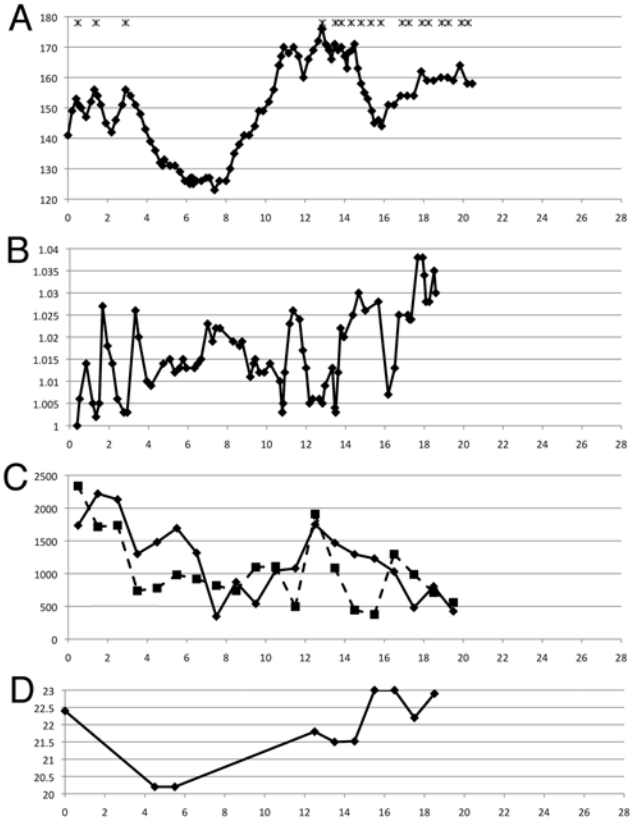

Fig. 3. Case 3. Sodium concentration **(A)** in mEq/L, urine specific gravity **(B)**, daily fluid intake *(solid line)* and daily fluid output *(dashed line)* in ml **(C)**, and weight in kg **(D)**. The values on the x axes indicate the postoperative days. *Asterisks* in panel **A** represent time of administration of DDAVP. Time zero for sodium concentration represents baseline sodium. Maximum sodium value was outside the range of recordable values of the laboratory test at its peak (> 176 mEq/L). Time zero for weight represents baseline dry weight.

99%, and 100% of lesion volume. The remaining patient (Case 2) underwent endoscopic surgery aimed at disconnection only.

Illustrative Case

Case 4

Presentation and Examination. This 3-year-old girl presented to our institution for management of a giant HH. Preoperatively, she had experienced 8–12 gelastic seizures per day since the 1st month of life. She had mild cognitive delay with expressive language being the most affected capacity on baseline neuropsychological and cognitive testing. She also exhibited behavioral symptoms including rage attacks and premature menarche at 16 months of age (treated with Lupron).

Operation. The patient underwent surgery via a transcallosal anterior interforniceal approach. Her HH is one of the largest lesions treated to date, with a maximum length of 3.6 cm and a volume of 20.4 cm^3 (Fig. 5). The lesion extended outside the third ventricle into the prepontine cistern directly adjacent to the basilar artery. Surgery proceeded uneventfully with the aid of stereotactic neuronavigation and intraoperative MR imaging; no additional resection took place after intraoperative MR imaging. The lesion was nearly totally resected (99%) (Fig. 5). Afterward, she was immediately extubated and taken to intensive care.

Postoperative Course. The patient experienced few postoperative neurological deficits after surgery and had minimal verbal output for the first 72 hours. She said "no" on Day 3 after surgery but remained aphasic for most of her hospitalization; at times, she would communicate, sometimes verbally, with her parents. She had left hemiparesis/neglect, which improved within the first few weeks after surgery. Anisocoria was present initially, but both pupils were reactive and her anisocoria resolved slowly during her stay. She maintained minimal eye contact with the examiner but would follow simple commands. On postoperative Day 7, she experienced an approximately 3-minute spell of lip-smacking and right-sided tonic posturing. She experienced several more seizures during the same day, which were attributed to hyponatremia given that these did not resemble her preoperative seizure semiology. She also was believed to experience an altered level of consciousness during hyponatremia with bouts of lethargy. Later during

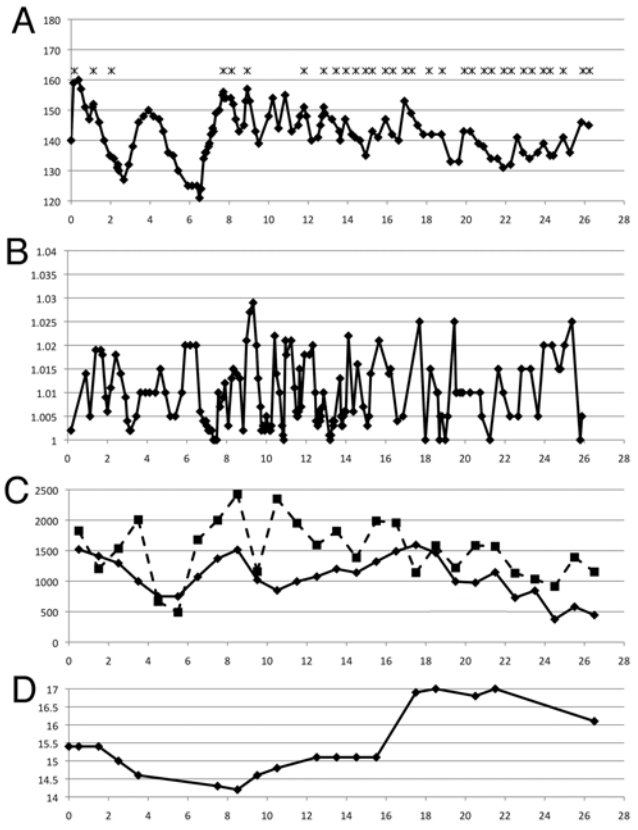

Fig. 4. Case 4. Sodium concentration **(A)** in mEq/L, urine specific gravity **(B)**, daily fluid intake *(solid line)* and daily fluid output *(dashed line)* in ml **(C)**, and weight in kg **(D)**. The values on the x axes indicate the postoperative days. *Asterisks* in **A** represent the time of administration of DDAVP. Time zero for sodium concentration represents baseline sodium. Time zero for weight represents baseline dry weight.

her hospitalization, once she was no longer hyponatremic, she also experienced staring spells but no overt seizures.

The patient's sodium values and other parameters are documented in Fig. 4. On postoperative Day 9, the sodium value returned to 152 mEq/L. Desmopressin was given intranasally and orally for all measured sodium values greater than 150 mEq/L. Generally speaking, our regimen starts with 2.5 μg of DDAVP intranasally, and we will increase this dose up to 10 μg intranasally if needed on a 1-time basis. Once patients are placed on standing DDAVP orders, we will administer doses between 50 and 100 μg orally twice daily. The patient was discharged 27 days following surgery after readmission to the pediatric ICU from a regular ward. She required DDAVP frequently throughout her hospitalization but did not receive any between Days 2 and 9, at which point she experienced 2 episodes of hyponatremia with a hypernatremic state in between. After her 2nd week of hospitalization, she continued to suffer from DI and required twice daily oral DDAVP, which at 2 points caused her to become hyponatremic. At the same time, she experienced central neurogenic hyperthermia during her hospitalization and required antiinflammatory medication on several occasions.

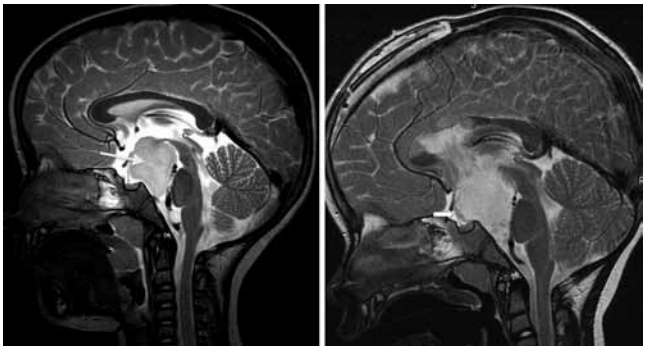

Fig. 5. Case 4. Sagittal T2-weighted MR images. **Left:** Preoperative image illustrating a giant HH *(arrow)* with components both inside and outside the third ventricle. **Right:** Postoperative image showing gross-total resection of this previously identified giant HH with a small rim of residual lesion anteriorly *(arrow)*.

After discharge from the hospital, this patient remained in neuro-rehabilitation for 1 month for ongoing physical therapy and then transferred to a subacute care center closer to home. She continued to have variations in her sodium measurements for several months. Her parents weighed every diaper and also measured all fluid intake to assist in managing her volume status, recording these in a spreadsheet. She required a peripherally inserted central catheter for intravenous medication and fluids upon returning to her home state.

At present, the patient is seizure free and is taking DDAVP 0.05 mg orally once nightly. She has experienced mild short-term memory loss since the surgery, and her language abilities remain slightly delayed, although she is in the 1st grade now and participates in all activities. She continues to undergo speech and language therapy. Her parents continue to maintain mild fluid restriction of free water to avoid precipitous decreases in her sodium levels. She undergoes blood sampling every 3 months now, and her sodium values hover above 150 mEq/L. She has not had a sodium value of less than 140 mEq/L in 2 years. Her appetite has been reported by her parents as insatiable, which triggers aggressive behavior related to taking food from others.

Discussion

It has been reported that DI can develop after pituitary region surgery in up to 75% of cases[7,8,12,15,17] and after transsphenoidal surgery in 10%–44% of cases,[4,6,12] whereas hyponatremia can occur in up to 35% of cases after surgery of pituitary region lesions.[12,13]

The management of hypernatremia and hyponatremia following pituitary or hypothalamic region surgery can often be complex and dependent on several variables. Following these types of surgeries, it is generally accepted that hypernatremia develops in response to decreased circulating levels of ADH in a process known as central DI. This can be caused by a lack of ADH secretion (after the appropriate stimulus) following such surgery and likely occurs from surgical disruption of the supraoptic and paraventricular nuclei of the hypothalamus, pituitary stalk, or posterior pituitary. We believe that one explanation for this effect in pediatric patients (such as those who have undergone HH surgery) involves the smaller circulating volume, perhaps evidenced by large shifts in serum sodium concentrations with minimal shifts in intake or output of fluids or

salts. It is also possible that HH is a secretory tissue, and removal results in deficits of hypothalamic-pituitary axis endocrine function responsible for normal sodium homeostasis, resulting in DI.

In contrast to hypernatremia, there are numerous etiologies for postoperative hyponatremia. Hyponatremia in this setting can be due to overzealous ADH administration (via DDAVP medication), a coinciding SIADH secretion caused by operative trauma,[2,12,13,16] or CSW, which is a state characterized by hypovolemia and poor resorption of sodium in the kidney. A prior report regarding pituitary surgery found that combined DI and hyponatremia proceeded with hypernatremia on the 1st–3rd postoperative days followed by hyponatremia during postoperative Days 7.5–10.[5] Another study reviewed (in rats) the so-called triphasic response that occurs after pituitary stalk sectioning: DI, followed by hyponatreria, and DI again.[16] These authors suggested, as did others, that leakage of vasopressin from damaged hypothalamiconeurohypophysial tracts and the posterior pituitary causes an "isolated second phase" (hyponatremia).[5,16] In other studies, hyponatremia has been previously shown not to be associated with high levels of ADH but rather associated with elevated ANP, thought to have a role in CSW, after pituitary region surgery.[12,18]

What likely happened in these 4 patients after resection of these very large tumors, most of which were removed aggressively, is a similar occurrence to the triphasic response. However, it is unclear and not possible to say with certainty that the hyponatremic states that occurred with the lowest values of sodium between Days 5 and 8 was due to CSW or SIADH. Whether high circulating ADH levels due to release from injured posterior pituitary cells caused SIADH in these patients as shown in the triphasic response in rats or high circulating values of ANP caused CSW is unknown here. More likely is that SIADH occurred given the overall weights of the patients when comparing discharge with baseline weight. Also, 2 additional periods ("double-dip") of hyponatremia cannot be explained by iatrogenic causes (that is, administration of DDAVP) in 2 of the 4 patients. One patient, in addition to experiencing a second decrease in sodium below the normal range, did have 2 hyponatremic episodes later during hospitalization that were attributable to DDAVP, likely from routine twice daily administration.

Management

We have not routinely measured urine osmolalities, urine free sodium, or fractional sodium excretion to evaluate hyponatremia and hypernatremia. We also have not measured central venous pressure in these young patients as a way of determining volume status, which may be more invasive and add an unnecessary risk. In contrast to extensive testing used by other authors in a prospective investigation into the causes of aberrations in sodium physiology after pituitary region surgery,[12] our management is described below. Those authors measured ADH levels, ANP levels, central venous pressure, creatinine clearance, free water resorption, fractional sodium excretion, and daily sodium output. They focused on central venous pressure as an indicator of the fluid volume resuscitation needed. They used free water resorption as a barometer to dictate DDAVP administration and used fractional sodium excretion as a way to monitor sodium replacement.

At our institution, patients are routinely monitored for hypernatremia or hyponatremia with serum sodium measurements every 6 hours, or more frequently when sodium values are more volatile. Input and output fluid parameters are measured hourly for urine output, oral intake, intravenous fluid intake, and other output such as emesis or bowel movements.

When patients are hypernatremic, in the setting of large amounts of dilute urine (specific gravity < 1.005) and sodium values are greater than 150 mEq/L, we place them on a regimen of DDAVP and encourage free water intake.

For patients who are hyponatremic, the management is more difficult and involves the assessment of volume status. Cerebral salt wasting requires vigorous salt replacement, whereas SIADH requires fluid restriction.[11] Fluid restriction, however, as well as diuretic use in symptomatic patients, was suggested by 1 group as the sole treatment of hyponatremia occurring after pituitary surgery if the sodium level is less than 130 mEq/L (given that their group believed it to be a form of SIADH).[5] The same group suggested that hyponatremia is the more troublesome of the 2 extremes and could lead to significant morbidity and mortality if untreated but also warned that 1 patient developed acute renal failure during a period of fluid restriction during a hyponatremic state (sodium level of 127 mEq/L).[5]

In addition to restricting fluid, we have used diuretics and saline replacement for treating hyponatremia. Saline replacement, however, is not without risk and can have iatrogenic consequences just as DDAVP can. Overaggressive treatment of hyponatremia can lead to central pontine myelinosis with correction of sodium too quickly. Correction of sodium at a rate of not more than 1 mEq/L every 2 hours has been our institutional goal. In those patients who can tolerate oral intake, salt tablets are also prescribed. Central pontine myelinosis was not observed in this cohort of patients.

Complications Associated With Hyponatremia

Two areas of concern related to hyponatremia include the development of seizures and the development of altered level of consciousness presumably due to cerebral edema and increased intracranial pressure. For this reason, if we have to err outside the normal range, we prefer for patients to be slightly hypernatremic rather than hyponatremic. We treated 3 patients who experienced seizures during their hyponatremic periods; 1 of these 3 patients also experienced a decreased level of consciousness. The patient in Case 1 experienced seizures within 48 hours of surgery of a tonic seizure semiology during a period of hyponatremia. Tonic seizures and gelastic seizures were part of her preoperative seizure semiology. The patient in Case 2 developed seizures during hyponatremia on postoperative Day 6 that were similar to previous gelastic seizures but also had episodes of staring to the right, with right nystagmus and left arm rhythmic movement followed by emesis. Seizures for the patient in Case 4 are described previously.

As stated, volume status in children (or adults) may

not be easy to quantify;[12] assessing the latency of peripheral capillary refill can be useful in demonstrating dehydration but remains a crude measurement. More invasive evaluations in children such as central venous pressure testing were forgone in our management. We recorded daily weights and measurements of input and output of fluids in these patients. Although they are also crude measures of volume status, these values can potentially predict a deficit or surplus in a patient's volume status, helpful in differentiating between salt wasting and SIADH. Daily weights, however, can be inconsistent or unreliable as can a reliable quantification of exact fluid input and output measurements.

The potential volatile nature of volume status in children, given a smaller circulating fluid volume, lends a possible explanation as to why the alternating values of high and low serum sodiums can occur so quickly in young patients; our impression is that small fluid shifts in children could potentially result in large changes in serum sodium (or other osmolality) values. A prior study found a trend for water electrolyte disturbances to tend to occur in younger patients but did not address the mechanism and suggested rather that it may occur since patients with hormone-producing pituitary tumors tend to be younger.[5]

Conclusions

We have shown that sequential alterations in hyponatremia and hypernatremia, previously demonstrated in pituitary region surgery, can occur in the largest of HHs. Careful management of this entity requires frequent assessment of sodium values, urine-specific gravity, and volume status. The determination of the cause of hyponatremia can be further demonstrated with laboratory testing of circulating ADH and ANP levels. The sodium homeostasis derangements demonstrated here seem to mimic the triphasic response; however, additional periods of hyponatremia independent of DDAVP administration that occurred here suggest that there is more to the phenomenon than is currently understood. A syndrome of alternating hypernatremia and hyponatremia after HH surgery seen here requires further investigation into the exact cause of hyponatremia occurring after HH surgery. It appears to be independent of DDAVP administration, but whether it is CSW, SIADH, or another possible abnormality related to removal of HH lesional tissue is not known. Although an HH often causes a pathological state of seizures, it potentially could serve a secretory role in normal physiological sodium homeostasis.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Abla, Ng. Acquisition of data: Abla, Kerrigan. Analysis and interpretation of data: Abla, Wait, Forbes, Ng. Drafting the article: Abla, Ng. Critically revising the article: Abla, Forbes, Kerrigan, Ng. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Abla, Kerrigan, Ng. Administrative/technical/material support: Abla, Wait, Forbes, Pati, Kerrigan, Ng. Study supervision: Abla, Kerrigan, Ng.

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