Neurosurgical hyponatremia: the role of inappropriate antidiuresis

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Of 80 consecutive neurosurgical patients, 23 exhibited inappropriate secretion of the antidiuretic hormone (ISADH); 11 of these patients required marked fluid restriction. Sodium concentration in the urine characteristically increased as serum values decreased. Only by following the urine sodium concentrations could the differential diagnosis of nutritional hyponatremia and ISADH be made. The role of ISADH in cerebral edema is stressed. The treatment recommended for ISADH is marked fluid restriction, whereas in nutritional hyponatremia, saline replacement is indicated.

KEY WORDS □ pituitary hormones □ osmoregulation □ hyponatremia □ antidiuretic hormone □ inappropriate antidiuresis □ brain edema □ head injury □ brain surgery

The syndrome of inappropriate secretion of antidiuretic hormone (ISADH) may occur with much greater frequency in neurosurgical patients than is generally appreciated. Furthermore, the water retention and serum hypo-osmolality that results from ISADH may contribute significantly to elevation of intracranial pressure. Interestingly enough, the therapy for this syndrome is fluid restriction, a routine measure in neurosurgery. In the full-blown syndrome, rigid fluid restriction of 500 cc or less per day usually initially may be required for the adult patient. But if the syndrome is recognized too late by the neurosurgeon, the patient may be critically ill due to "overhydration" with 1500 to 3000 cc per 24 hours, the latter not uncommonly occurring when one adds the fluids given by the anesthesiologist to those ordered by the house staff during the first 24 hours following surgery.

The syndrome of ISADH results from continued secretion of antidiuretic hormone (ADH) in the face of low serum osmolality and an expanded extracellular fluid volume (ECFV). Thus the term "inappropriate antidiuresis" is used, for under these conditions the hypothalamic neurons should be inhibited and ADH release suppressed. In this syndrome, however, ADH excess induces water retention by the kidney to the point of hypotonic expansion of ECFV and a secondary natriuresis.

The classical features of this syndrome are:
1. Low serum sodium (< 135 mEq/L)
2. Low serum osmolality (< 280 mOsm/kg)
3. High urine sodium (> 25 mEq/L)
4. Urine osmolality > plasma osmolality

*Osmolarity is the number of milliosmols or mOsm per liter of solution. Osmolality is the number of mOsm per kg of solvent (in this case, water) and is measured by the freezing point depression method: 1000 mOsm/kg of water reduces the freezing point 1.86° C. Serum osmolality normally ranges between 280 and 300 mOsm/kg, or roughly twice the m/EqL of the Na ion.
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5. Urinary sodium wasting not due to renal or adrenal disease
6. Absence of peripheral edema or dehydration
7. Poor response to hypertonic saline.

We are reporting a clinical study of this phenomenon in 23 neurosurgical patients.

Method and Materials

A series of 80 consecutive patients were studied at the Veterans Administration Hospital and the George Washington University Hospital for evidence of ISADH. Preoperative and postoperative studies were carried out. These were concluded 7 days after surgery or when no further evidence of ISADH was seen.

The workup called for the following studies: daily serum electrolytes, blood urea nitrogen (BUN), creatinine, osmolality; daily hematocrits; daily 24-hour urine electrolytes, osmolality, and specific gravity. Electrolytes and BUN were measured on the Technicon SMA-12 Auto-analyzer. Osmolality was measured by the freezing point depression method with an Advanced Osmometer. The general medical status including state of hydration was noted. Changes in neurological signs, especially those indicating increased intracranial pressure, were recorded. Medications, other procedures such as tracheostomy, and fluid intake and output were noted. Accurate daily weights were not obtained routinely. Patients with evidence of kidney disease (salt-losing nephritis) or other medical conditions causing water retention and hyponatremia were not included.

Results

Table 1 summarizes some of our findings in the 80 cases studied. Twenty-three patients (29%) had findings clearly consistent with ISADH, 11 severe, 12 mild. The severe cases failed to respond to saline infusion but did respond to rigid fluid restriction (300 to 600 cc daily). The 12 mild cases only showed the syndrome for a few days and did not require drastic fluid restriction.

Among the remaining, 57 patients were categorically excluded. There were 26 whose serum sodium dropped following the surgical procedure. In 19 of these cases there was a strong suspicion that sustained ADH secretion occurred, causing a dilutional reduction in serum [Na]. Therefore, although they were excluded from the ISADH category, the difference in these 19 additional cases may be only one of degree. They included 6 subdural hematomas, 3 aneurysms, 2 metastatic pulmonary carcinomas, 4 intracerebral hematomas, 2 meningiomas, 1 cholesteatoma, and 1 cribiform plate repair.

Discussion

The pathogenetic sequence of this syndrome in the neurosurgical patient and its probable role in cerebral edema is shown in Fig. 1. The most likely explanation for failure of the kidney to conserve sodium in the face of a low serum sodium concentration [Na] is believed to be depression of proximal renal tubular reabsorption of sodium in response to expansion of ECFV. In other words, the homeostatic mechanisms of the body are attempting to correct ECFV by excreting Na, which normally would take water with it. However, in the latter condition water retention occurs because of the effect of ADH.

Provided other causes of low serum [Na] and osmolality with high urine sodium excretion reasonably can be excluded, the diagnosis of ISADH should be suspected on the basis of sodium and osmolality findings in serum and urine. Total body Na in some instances actually may be somewhat increased if the amount of Na in the expanded ECFV compensates for the low serum sodium, particularly if the adrenal axis has been stressed by trauma or surgery. In a normal subject given ADH, an increase in body weight will occur due to water retention, but surgical patients may lose weight as some catabolic water is lost. From the diagnostic standpoint, the ideal test would be stressing the patient with a water load and look for failure to undergo a normal diuresis. This may improve with administration of ethanol in certain forms of this syndrome. However, reasons for avoiding this test in our patients are obvious.

Bakay and Lee stated, “Dehydration of the patient by withholding fluids or severely limiting the fluid intake is pointless in the presence of cerebral edema. Such measures completely fail to have any effect on the edema of the brain, while on the other hand they would have disastrous effects on the ho-
### TABLE 1
Cases demonstrating inappropriate secretion of antidiuretic hormone (ISADH)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Diagnosis</th>
<th>Serum Sodium</th>
<th>Urine Sodium</th>
<th>Serum Osmolality</th>
<th>Urine Osmolality</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>subacute subdural hematoma, removed</td>
<td>118-125</td>
<td>39-90</td>
<td>not done</td>
<td>not done</td>
<td>ISADH began 7 days after head injury and 1 day before surgery simultaneous with onset of stupor; lasted 8 days; unresponsive to saline; responded to 500 cc daily intake; preop serum sodium = 133; no steroids.</td>
</tr>
<tr>
<td>2</td>
<td>acute capsular intracerebral hematoma, spontaneons, removed</td>
<td>123-132</td>
<td>71</td>
<td>258</td>
<td>786</td>
<td>ISADH began 1st postop day; lasted 5 days; unresponsive to saline; responded to 500 cc daily intake; ISADH worse on 2nd postop day when patient became less responsive; preop serum sodium = 142; on steroids.</td>
</tr>
<tr>
<td>7</td>
<td>metastatic CA, parietal, excised, from lung (7)</td>
<td>123-132</td>
<td>64</td>
<td>255-266</td>
<td>not done</td>
<td>ISADH began 1st postop day, lasted 3 days; not treated; preop serum sodium = 140; on steroids.</td>
</tr>
<tr>
<td>8</td>
<td>acute subdural hematoma, removed</td>
<td>123-133</td>
<td>33-150</td>
<td>240-273</td>
<td>476-785</td>
<td>ISADH began 5th post head injury day in hospital, lasted 16 days; unresponsive to saline; responded to 300 cc daily intake; 1st postop day: nutritional hypotension indicated by low urinary sodium; preop serum sodium = 140; on steroids.</td>
</tr>
<tr>
<td>9</td>
<td>glioblastoma, temporal, excised</td>
<td>131-133</td>
<td>29</td>
<td>273</td>
<td>420</td>
<td>mild ISADH on 1st postop day only; not treated; preop serum sodium = 138; on steroids.</td>
</tr>
<tr>
<td>11</td>
<td>subacute subdural hematoma, removed</td>
<td>119-128</td>
<td>43-145</td>
<td>238-272</td>
<td>200-1030</td>
<td>ISADH on admission, lasted 12 days; unresponsive to saline; responded to 500 cc intake; patient most obtunded when ISADH maximum; ISADH recurred 3 days later when lapsed into stupor; lasted 17 more days; excess fluid restriction precipitated transient anuria with high BUN and creatinine; no steroids.</td>
</tr>
<tr>
<td>17</td>
<td>acute subdural hematoma, removed</td>
<td>132</td>
<td>106</td>
<td>276</td>
<td>736</td>
<td>mild ISADH on 2nd postop day only; not treated, preop serum sodium = 139; on steroids.</td>
</tr>
<tr>
<td>18</td>
<td>metastatic CA from lung, occipital, excised</td>
<td>130-132</td>
<td>44-76</td>
<td>268-269</td>
<td>524-789</td>
<td>ISADH began 1st postop day, lasted 9 days; not treated; preop serum sodium = 134; on steroids.</td>
</tr>
<tr>
<td>21</td>
<td>subacute subdural hematoma, removed</td>
<td>129-132</td>
<td>72-91</td>
<td>265-266</td>
<td>550-560</td>
<td>ISADH on 2nd and 3rd postop days only; not treated; preop serum sodium = 135; on steroids.</td>
</tr>
<tr>
<td>25</td>
<td>chronic subdural hematoma, removed</td>
<td>133</td>
<td>99</td>
<td>270</td>
<td>591</td>
<td>mild ISADH on 2nd postop day only; not treated, no preop serum sodium; on steroids.</td>
</tr>
<tr>
<td>30</td>
<td>subacute intratemporal hematoma, spontaneous, removed</td>
<td>129-134</td>
<td>76-252</td>
<td>262-270</td>
<td>709-942</td>
<td>ISADH present on admission, lasted 7 days preop and 7 days postop; not treated; no steroids.</td>
</tr>
<tr>
<td>32</td>
<td>chronic subdural hematoma, removed</td>
<td>132</td>
<td>153</td>
<td>273</td>
<td>980</td>
<td>mild ISADH on 1st postop day only; not treated; preop serum sodium = 133; no steroids.</td>
</tr>
<tr>
<td>34</td>
<td>bullet, excised</td>
<td>130-133</td>
<td>34-42</td>
<td>—</td>
<td>—</td>
<td>mild ISADH on 1st two postop days only; not treated; preop serum sodium = 137; no steroids.</td>
</tr>
<tr>
<td>36</td>
<td>chronic subdural hematoma, removed</td>
<td>130-133</td>
<td>57-77</td>
<td>277-285</td>
<td>396-481</td>
<td>mild ISADH on first 3 postop days; not treated; preop serum sodium = 134; no steroids.</td>
</tr>
<tr>
<td>41</td>
<td>meningioma, parietal, excised</td>
<td>130</td>
<td>108</td>
<td>275</td>
<td>447</td>
<td>mild ISADH on 1st postop day only; not treated; preop serum sodium = 137; on steroids.</td>
</tr>
<tr>
<td>46</td>
<td>ruptured ACA aneurysm, ligated</td>
<td>119-131</td>
<td>26-132</td>
<td>251-282</td>
<td>294-620</td>
<td>ISADH began 5 days post bleed (13 days preop), lasted 15 days; responded to 500 cc daily intake; recurred 6 days later (8th postop day) when patient became less responsive; lasted 7 days; reappeared to fluid restriction; on steroids.</td>
</tr>
</tbody>
</table>
TABLE 1 (continued)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Diagnosis</th>
<th>mEq/L</th>
<th>mOsm/kg</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55</td>
<td>acoustic neurinoma, excised</td>
<td>122-132</td>
<td>57-131</td>
<td>ISADH began 1st postop day, lasted 18 days; unresponsive to saline; responded to 900 cc daily intake; meningitis; preop serum sodium = 136; on steroids.</td>
</tr>
<tr>
<td>56</td>
<td>chronic subdural hematoma; removed</td>
<td>126-132</td>
<td>34-76</td>
<td>ISADH began 1st postop day, lasted 7 days; responded to 400-900 cc daily intake; diabetes explains elevated serum osmolality; preop serum sodium = 139; no steroids.</td>
</tr>
<tr>
<td>57</td>
<td>chronic subdural hematoma; removed</td>
<td>125-133</td>
<td>33-68</td>
<td>ISADH began 1st postop day, lasted 7 days; responded to 900 cc intake; preop serum sodium = 139; no steroids.</td>
</tr>
<tr>
<td>60</td>
<td>acute and chronic subdural hematoma; removed</td>
<td>132</td>
<td>150</td>
<td>ISADH on admission, lasted 23 days; unresponsive to saline; responded to 400-800 cc daily intake; preop serum sodium = 137; no steroids.</td>
</tr>
<tr>
<td>63</td>
<td>chronic subdural hematoma; removed</td>
<td>126-132</td>
<td>77-201</td>
<td>ISADH on admission, lasted 6th postop day, lasted 20 days; unresponsive to saline; responded to 400-900 cc daily intake; preop serum sodium = 135; no steroids.</td>
</tr>
<tr>
<td>65</td>
<td>subacute subdural hematoma, removed</td>
<td>116-127</td>
<td>34-118</td>
<td>ISADH on admission, lasted 7 days; responded to 700-1300 cc daily intake; preop serum sodium = 128; no steroids.</td>
</tr>
</tbody>
</table>

meostasis of these already critically ill patients." The significant word here is "dehydration." It is probably true that these patients should not be dehydrated, but it is also true that fluid restriction to prevent overhydration in these postoperative patients is not only customary but, in many cases, mandatory. Fluid retained and salt lost by the kidneys as a result of sustained ADH secretion will dilute the vascular solutes and create an unfavorable osmotic gradient across the blood-brain interface. Since sodium and chloride normally contribute about 250 mOsm/kg of the 290 mOsm/kg found in human plasma, a reduction in serum [Na] may have a significant effect on increasing the chances of cerebral edema. Thus in neurosurgical patients another vicious cycle of increasing intracranial pressure is evident (Fig. 1).19

Surgeons have known for years that overnight dehydration, pain, narcotics and barbiturates, anesthesia, and surgical stress tend to cause postoperative fluid retention and hyponatremia. This may be due to a combination of factors including adrenal stimulation resulting in salt retention and hence secondary water retention and/or posterior pituitary stimulation with primary water retention. Secretion of ADH is stimulated in patients undergoing anesthesia and surgery.1,2,7,10,12,13,25,27,38-35,44-46,60,61 These studies show that the postoperative patient is unable to handle large water loads due to the tendency for kidneys to retain water.

Disease entities in which ISADH is seen...
include central nervous system problems, pneumonitis, pulmonary tuberculosis and aspergillosis, thymoma, carcinoma of the lung, duodenum, and pancreas, and idiopathic causes. The frequent occurrence of ISADH with carcinoma of the lung is an important factor, for it may aggravate cerebral edema during intracranial surgery for metastases from the lung.

The inappropriate ADH syndrome often complicating neurological disorders previously have been called "cerebral hyponatremia" or "cerebral salt wasting." Some case reports of ISADH are associated with head injury. Other case reports associated with ISADH have included brain neoplasms, Guillain-Barre syndrome, convulsive seizure disorder, subarachnoid hemorrhage from aneurysm, meningitis, encephalitis, poliomyelitis, intracerebral hemorrhage, cerebral infarction and acute obstruction of ventriculoatrial shunts.

Wise felt that plasma hypotonicity was common after brain surgery or head injury but that ISADH did not often occur. He reported seven cases of low serum [Na] following craniotomy, but did not include urine [Na] and osmolality studies and made no mention of inappropriate ADH secretion as an etiological factor. In his text on fluid and electrolytes in neurological surgery, Wise noted that after craniotomy there usually is greater retention of water than sodium for 2 to 5 days. For this reason he recommended restricting daily intake to 1500 to 2000 cc (including about 500 cc of dextrose in half-normal saline) on the first and second postoperative days for the average adult patient.

McLaurin and his associates have made extensive metabolic and electrolyte studies on head injury and craniotomy patients. Whereas they indicated that their studies failed to show any significant incidence of ISADH, a review of their data seems to show that ISADH may indeed have been fairly common. Certainly their study published in 1961 showed that post-craniotomy patients are poorly able to handle significant water loads. In 10 patients receiving 2000 to 4000 cc of glucose and water daily, seven showed mild to marked signs of water intoxication and a drop in serum [Na] within the first 48 to 72 hours after surgery.

In 1952 Zimmerman and Wangensteen had reported similar results in general surgical patients. In reviewing their data on 14 head injury patients, McLaurin stated that the serum sodium concentration frequently dropped to 130 to 135 mEq/L and occasionally below 130 mEq/L. This occurred in the face of 24-hour urine sodium values averaging 43 mEq on day 1, 59 mEq on day 2, 90 mEq on day 3, 103 mEq on day 4, and 102 mEq on day 5.

While it is possible that part of the hyponatremia may be secondary to a shift of Na from the extracellular fluid into the cell, it also is very likely that much of it is dilutional due to water retention secondary to excess ADH production. If a defect in the excretion of water occurs in the absence of a sodium retaining state (as in hypovolemia, dehydration, edema) and the presence of hyponatremia, one must strongly suspect ISADH. If we couple this with evidence of urinary sodium excretion, then this is strong presumptive evidence for the inappropriate ADH syndrome.

The effects of glucocorticoids must be considered in these patients. Although this factor was not controlled in this study, there was no consistent difference between the 44 (of 80 cases) who received methylprednisolone and the remainder who did not. It is possible that these steroids may increase tissue catabolism and release fluid into the extracellular space, thus diluting serum Na. However, as noted below, their renal and posterior pituitary effects, would tend to have the opposite effect on serum [Na].

In a separate study of methylprednisolone in intracranial surgery we followed postoperative electrolytes on 50 patients. In none of these was there any elevation in serum sodium concentration but 15% had serum [Na] of 126 to 132 mEq/L in spite of large doses of corticosteroids. In nine cases of brain tumor Shenkin and Gutterman studied effects of dexamethasone and found lowered serum [Na]. They found a loss of body weight and extracellular fluid and thought the steroids were causing greater urine output. This would be consistent with the known tendency for glucocorticoids to suppress ADH secretion and increase free water clearance by the kidney. However, Fichman and Bethune found that dexam-
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methasone had no significant effect on salt or water balance in cases with ISADH. Many of our patients received diphenylhydantoin, but there was no obvious effect. Intravenous diphenylhydantoin will suppress ADH secretion in some patients with ISADH, but routine oral or intramuscular administration has no significant influence. It is interesting that 15 of 23 cases of ISADH had subdural hematomas. Nine had severe ISADH, and six were mild.

Regardless of the precise cause of this phenomenon, it is important to be aware of its frequency in neurosurgical patients. We believe it occurs more commonly than the neurosurgical literature indicates. In our series of 80 patients, 29% showed definite evidence of ISADH, and 14% of the 80 patients required marked fluid restriction, especially cases of subdural hematoma. About 60% of the 80 cases had a reduction in serum Na. Accordingly, we propose that routine pre- and postoperative measurements of serum and urine electrolytes and osmolality be carried out on patients undergoing brain surgery as well as patients suffering from head injury, intracranial hemorrhage, or other brain lesions. The postoperative studies should be run serially for as long as abnormalities exist.

If both serum and urine [Na] are low, the patient probably needs salt. However, if the urine [Na] is consistently over 25 mEq/L, then fluid restriction, the treatment of choice for ISADH, is in order. This simple guideline assumes that other less common causes of electrolyte imbalance are excluded. If the hyponatremia is moderate (120–130 mEq/L) and ISADH exists, then it only may be necessary to restrict fluid intake to approximately 600 cc daily or 25 cc/hr until serum [Na] improves. On the other hand, if the hyponatremia is so severe that signs of increasing central nervous system deficit develop, it also may be necessary to carefully administer hypertonic saline to avoid further cerebral injury. The recommended dosage is 6 ml of 5% sodium chloride solution per kilogram of adult body weight, which will raise the serum [Na] about 10 mEq/L. For children, 3% saline solution is preferred. However such a degree of hyponatremia should not occur in the properly managed patient. In any event, fluid and electrolyte therapy must be individualized, flexible, and frequently assessed by its effects on serum [Na] and renal function. These observations raise the question of what routine fluid therapy should be used on craniotomy patients. A severe restriction to 600 cc per day as advocated by Fay for certain head injury patients may be excessive in many cases. For adult patients we now tend to follow the practice of giving about 400 to 500 cc per 8 hours. This essentially is the recommendation of Bakay, et al. However, after the first 24 hours, the fluid orders for subsequent days are determined by the laboratory findings and clinical state of the patient as previously outlined. We used to restrict salt since many of our patients receive corticosteroids, but now we find any elevation of serum [Na] unusual and have returned to the use of 5% dextrose in half-normal (0.45%) sodium chloride solution regardless of whether the patient is receiving corticosteroids for brain edema control. Since it is hazardous to use hypotonic solutions (such as half-normal saline after metabolism of glucose) in any patient who is hyponatremic or likely to become so, one must consider the use of 5% dextrose in normal saline (or its equivalent) in such patients. It is essential to include the fluids received during anesthesia in the restricted first 24-hour postoperative intake. Moreover, since patients receive nothing by mouth for several hours prior to surgery, it is possible that this may stimulate ADH production which persists after the surgical stress. Perhaps these patients should receive some intravenous fluids the night prior to surgery.

An important measurement not commonly made on neurosurgical patients is the central venous pressure (CVP). If ISADH is present and the patient is receiving excess fluid, this pressure may be high. On the other hand if fluid intake is overly restricted, the CVP will fall to low levels. The use of blood volume or ECFV measurements should be considered in special cases. One must avoid precipitating oliguria and a rising BUN with fluid restriction in patients having marginal kidney function; this occurred in three of our patients. Excess fluid restriction must be avoided in patients whose preoperative BUN is marginally elevated. One must
also be aware of a high urine output (such as may occur with a transient posterior pituitary insufficiency) and/or sweating in excess of fluid intake. If persistent in the unconscious patient, this may precipitate a sudden and irreversible rise in BUN and serum [Na].

It is quite apparent that the margin for error with fluid and electrolyte balance in either direction is sharply curtailed in many neurosurgical patients. Appropriate treatment requires appropriate monitoring and awareness. Thus, the success of brain surgery often may depend less on a knowledge of classical neurophysiology than of the general physiology of body organ systems.

Summary

We have studied 80 consecutive neurosurgical patients with brain lesions for evaluation of the inappropriate secretion of antidiuretic hormone (ISADH). All but two underwent brain surgery. We found 23 patients (29%) exhibiting this syndrome of fluid retention. In 11 patients (14%) the syndrome was marked. Basically the diagnosis was made by demonstration of an inappropriately high urine osmolality and sodium concentration in the face of a low serum osmolality and sodium concentration. Other causes of hyponatremia such as inadequate salt intake, salt-losing nephritis, hypoadrenalism, cirrhosis, and cardiac failure were ruled out. All but 31 of the remaining patients demonstrated a significant drop in serum sodium concentration but without the other signs of classical ISADH. Some of these were secondary to sodium depletion but water retention by the kidneys in response to excess ADH secretion may still have played a role.

Evidence for ISADH occurrence with general anesthesia, general surgery, carcinoma of the lung, and cerebral trauma is reviewed. It is suggested that all these factors may combine to create a significant incidence of ISADH in craniotomy patients. Since there is a lowering of plasma osmotic pressure with reduction of sodium concentration, this phenomenon may be another important contributor to brain edema in the early post-craniotomy days.

We have made suggestions for certain routine measurements in craniotomy or head injury patients. The fluid and electrolyte therapy for these patients is presented and the treatment of ISADH, which basically is marked fluid restriction, described.

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