Occult Pulmonary Malignancy in Syndrome of Inappropriate ADH Secretion with Normal ADH Levels*

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Although the syndrome of inappropriate ADH secretion (SIADH) has many causes, principally pulmonary, central nervous system or neoplastic disease, and drugs, patients may present with SIADH in whom the etiology is not readily evident. We measured serum ADH levels in such an individual in both the eunatremic and water-loaded states and found levels to be undetectable despite failure to dilute the urine. A small oat cell pulmonary carcinoma was ultimately diagnosed with lung tomograms and cytology. Following a partial response to water restriction, demeclocycline was effective in producing a water diuresis that restored the serum sodium concentration to normal. Patients with clinical SIADH but low serum ADH levels can harbor a malignant or benign process that, notwithstanding the low ADH levels, may still remain responsive to demeclocycline, suggesting either nonproductive secretion of a biologically-active, immunologically-inactive ADH-like peptide, or increased renal tubular sensitivity to ADH.

Elevated plasma antidiuretic hormone (ADH) levels have been documented by radioimmunoassay in the clinical setting of most patients with the syndrome of inappropriate ADH secretion (SIADH), including that associated with neoplastic disease. Certain pulmonary malignancies,12 as well as nonmalignant syndromes,5,9 have the propensity to produce substances with hormonal biologic activity but not necessarily immunologic activity in RIA assays. Robertson and colleagues9 and Zerbe et al11 reported that 10 percent of patients with clinical evidence of SIADH exhibit suppressed vasopressin levels. These investigators proposed that such patients might elaborate an antidiuretic substance unrecognized by the ADH immunoassay. We observed a patient with hyponatremia, SIADH, but undetectable ADH immunologic activity. Clinical and laboratory findings suggested that our patient was secreting an unidentified substance with antidiuretic properties, producing systemic hyponatremia which may have suppressed secretion of immunologically normal ADH. Subsequently, a small pulmonary oat cell carcinoma was detected. Like the SIADH counterparts with high ADH levels, this patient similarly responded to demeclocycline with a decrease in urinary concentration.

CASE REPORT

A 55-year-old white man was transferred to the San Diego Veterans Administration Hospital for treatment of chronic osteomyelitis of the left tibia. This infection originated from a compound fracture incurred in a motor vehicle accident 15 months earlier. Other important history included amitriptyline therapy for depression, which was continued during the initial phase of hospitalization. Despite surgery and antibiotics, the patient's osteomyelitis did not heal over a three-month period in the hospital. He then exhibited the new onset of weakness and lethargy for five days.

The patient was a thin, lethargic man in no acute distress. Supine and seated blood pressure levels were 130/90 mm Hg and 125/95 mm Hg, respectively. The pulse rate was 85 in both lying and seated positions. He was afebrile and the respiratory rate was 12/min. Results of the remainder of the physical examination were unremarkable except for a plaster cast on the left leg and the aforementioned lethargy. Laboratory data included the following serum values: sodium, 109 mEq/liter; chloride, 75 mEq/liter; potassium, 4.0 mEq/liter; bicarbonate, 24 mEq/liter; blood urea nitrogen, 14 mg/dl; creatinine, 1.2 mg/dl; blood glucose, 110 mg/dl; cholesterol, 200 mg/dl; triglycerides, 155 mg/dl; albumin, 4 g/dl; globulins, 3.5 g/dl; SCOT, 30 IU/liter; osmolality, 290 mOsm/kg H2O. The 24-hour urinary sodium excretion was 73 mEq/liter with a volume of 1.5 liters and the urinary osmolality was 405 mOsm/kg H2O. Morning serum specimens contained normal amounts of cortisol and thyroxine. All other studies were unremarkable, including a normal heart size on chest film.

The syndrome of IADH was suspected and amitriptyline was discontinued as a possible causative agent. Treatment consisted of fluid restriction, furosemide, and intravenous saline solution. With this regimen, body weight decreased by 2 kg and the serum sodium concentration increased to 123 mEq/liter during a two-day interval. Further rigorous fluid restriction produced a serum sodium concentration of 136 mEq/liter and a random serum ADH concentration of 0.4 µU/liter by three days. To better evaluate this situation, additional tests were performed (see below).

After completion of the diagnostic evaluation and while awaiting ADH quantitation, we treated the patient with oral demeclocycline (900 mg/day) and modest fluid restriction. After 24 hours, urinary osmolality decreased to 100 mOsm/kg H2O and after 72 hours, the serum sodium concentration increased to 138 mEq/liter. The results of multiple sputum examinations demonstrated cells that were diagnostic for oat cell carcinoma of the lung, and subsequent tomograms of the chest revealed a small density in the peripheral portion of the left upper lobe of the lung. The patient refused further diagnostic or therapeutic procedures. He succumbed to his malignancy six months later.

Diagnostic Studies

Expecting to find high baseline ADH levels and in order to determine their suppressibility, the patient underwent an intravenous water load of 5 percent dextrose in water (20 ml/kg), as described by DeFronzo and colleagues.6 We performed measurements of serum sodium, osmolality, and antidiuretic hormone at baseline and hourly for four hours.

In addition, we determined urinary osmolality and volume at baseline and at four hours. Since the patient did not void, we were unable to determine these latter measurements more frequently.

Chemical Methods

Antidiuretic hormone was measured by radioimmunoassay as previously described.9 The lower limit of sensitivity of the ADH RIA is 0.19 µU/ml. Since the ADH radioimmunoassay had only 0.4 percent cross reaction with vasotocin, we elected to quantitate this peptide by a different immunoassay employing an initial chromatographic separation, as previously described.8 Reproducibility of the vasopressin measurements was determined by replicate analysis of single samples. The intra-assay coefficient of variation for the vasopressin RIA was 7.1 percent, and the interassay coefficient of variation was 14.9 percent. All other tests were done in the hospital laboratories using established automated techniques.
Table 1—Results of Water Loading (1500 ml)

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>1 Hour</th>
<th>2 Hours</th>
<th>3 Hours</th>
<th>4 Hours</th>
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<tbody>
<tr>
<td>(Serum)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Antidiuretic Hormone*</td>
<td>0.19</td>
<td>0.20</td>
<td>0.31</td>
<td>0.20</td>
<td>0.32</td>
</tr>
<tr>
<td>Osmolality†</td>
<td>275.0</td>
<td>265.0</td>
<td>261.0</td>
<td>264.0</td>
<td>264.0</td>
</tr>
<tr>
<td>Na (mEq/Liter)</td>
<td>135.0</td>
<td>130.0</td>
<td>129.0</td>
<td>130.0</td>
<td>130.0</td>
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<tr>
<td>(Urine)</td>
<td></td>
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<tr>
<td>Osmolality</td>
<td>974.0</td>
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<tr>
<td>(mOsm/kg H2O)</td>
<td></td>
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<tr>
<td>Na</td>
<td>310.0</td>
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<tr>
<td>(mEq/Liter)</td>
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<tr>
<td>Volume (ml)</td>
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Free water clearance = –3 ml/min
*normal >1.2 μU/ml
†normal 280-289 mOsm/kg H2O

RESULTS

Random plasma ADH was 0.4 μU/ml with a serum sodium concentration of 136 mEq/liter. The data summarized in Table 1 represent the laboratory values during the intravenous water load. Plasma osmolality was initially low and dropped even further during the fluid challenge. Despite a persistent markedly concentrated urine and failure to achieve a positive free water clearance, plasma ADH concentrations remained low throughout the four-hour study period. Arginine vasotocin also was unmeasurable, and the value was less than 0.4 μU/ml, the lower limit of sensitivity for this assay.

DISCUSSION

A complete discussion of the causes of hyponatremia is beyond the scope of this manuscript. However, we have excluded all but one of the common etiologies in our patient. Specifically, he had normal thyroid, cardiac, hepatic, renal, and adrenal function using standard clinical and laboratory criteria. The normal blood pressure and pulse in the supine and seated positions appears to eliminate significant volume depletion, and the therapeutic response after demeclocycline does not suggest hypovolemia. In addition, the failure to experience diuresis following the water challenge and further lowering of the plasma osmolality eliminates the possibility of a reset osmostat producing the hyponatremia (either by lowering the osmotic threshold or direct neoplastic baroreceptor invasion). Therefore, it is reasonable to assume that the patient had the clinical and the laboratory findings of SIADH. This hypothesis is supported further by the subsequent diagnosis of oat cell carcinoma of the lung, the most common neoplasm associated with ectopic ADH production.

Levels of circulating ADH vary with posture, ambulation, degree of hydration and baroreceptor integrity, but in subjects with normal serum osmolality, values in excess of 1.2 μU/ml are usually found. This level will fall when serum osmolality falls below 275 mOsm/kg H2O, and the physiologic effects of circulating ADH diminish. Despite the great sensitivity of the assay, levels of circulating ADH found in our patient before water loading, at a serum sodium concentration of 135 mEq/L and urine osmolality of 974 mOsm/kg H2O were negligible. Serum ADH levels were also unmeasurable during hyponatremia and urinary hyperconcentration. These observations in a patient with clinical SIADH strongly suggest suppression of endogenous ADH and eliminate the possibility that the patient was secreting normal human ADH from the pituitary gland or an ectopic source. The suggestion is that he was secreting another substance with ADH-like biologic activity, but lacking immunologic identity in the radioimmunoassay, as has been suggested by similar cases previously reported.

Despite the fluid challenge and concomitant decrease in serum sodium concentration, our patient excreted only a fraction of the administered water load while maintaining a urinary osmolality greater than 900 mOsm/liter, evidence of continued end-organ antidiuretic effect. This observation, together with the aforementioned ADH measurements, again implicates the excretion of an unidentified factor with antidiuretic biologic activity. Our radioimmunoassay determinations have eliminated consideration of arginine vasotocin, but further characterization was not possible. An alternative possibility would be an increased renal sensitivity to small amounts of circulating ADH. We cannot exclude this hypothetical possibility, although it is unlikely that such a condition would appear so rapidly. Thus, the patient was similar to the group of subjects mentioned previously by Robertson and colleagues who had SIADH and suppressed levels of circulating ADH. While the etiology may be benign or malignant, the presence of an underlying tumor in such cases must be considered; however, not all such cases have been associated with underlying neoplasms.

The patient with SIADH should be treated for the specific etiology of the hyponatremia if possible. Patients unable or unwilling to adequately restrict water intake have, in the conventional cases of those with high circulating levels of ADH, been treated successfully with demeclocycline. Although a response to the discontinuation of amitriptyline cannot be excluded, we believe that we have obtained a response to demeclocycline in the present case with undetectable ADH levels. He was able to dilute his urine to an osmolality of 100 mOsm/kg H2O, and he maintained eu-natremia with only modest fluid restriction. This response suggests that there exists a biophysically common ADH receptor for the various immunologic ADH species and whose biologic effect is in some way inhibited by demeclocycline therapy.

REFERENCES

Errant Placement of Nasoenteric Tubes*

A Hazard In Obtunded Patients

Jack Ende, M.D.; Gordon L. Snider, M.D., F.C.C.P.; and
Dennis J. Beer, M.D.†

We describe a case of intubation of both main-stem bronchi
with a narrow-bore nasoenteric tube on two separate
occasions, with the subsequent development of pleural
effusions of enteral solution, in an elderly semicomatose
woman with a properly positioned cuffed endotracheal tube.
Neither aspiration of fluid from the tube nor propulsion
of air with auscultation of gastric borborygmi are
positive proof of proper positioning. We recommend that in
obtunded patients, especially if there is the possibility of
impaired mucosal integrity, appropriate placement of the
tube should be confirmed by chest roentgenogram.

The placement of nasoenteric tubes is commonplace in
current management of critically or chronically ill pa-
tients. Minor complications such as nasal mucosal abrasions
are common, while more pernicious complications, including
cranial penetration,1 a pharyngeal dissection,2 esophageal
or gastric perforation,2,3 and endotracheal passage with
respiratory decompensation and pleural penetration,4,5
occur more rarely. With the introduction of thin narrow-bore
feeding tubes, the complications of errant tube placement
would seem less likely, although they are not eliminated.
Knowledge of the warning signs indicating faulty placement
is necessary if serious complications are to be avoided.
The early recognition of misplacement of the tube may then avert
the development of more serious complications. We report a
case of intubation of both main-stem bronchi with a naso-
enteric tube on two separate occasions, with the subsequent
development of pleural effusions of enteral solution in an
obtunded elderly woman with a properly positioned cuffed
endotracheal tube.

CASE REPORT

A 92-year-old woman with a history of congestive heart failure,
mild chronic renal insufficiency, and emphysema with moderate
limitation of airflow was hospitalized because of pain in the chest wall
sustained after a fall. Physical examination revealed a large ecchy-
motic region over the left hemithorax, with decreased breath sounds
over the left base posteriorly. The chest roentgenogram taken on
admission demonstrated left lower lobe atelectasis. The patient
developed a cough productive of mucopurulent sputum; Gram's
stain showed Gram-negative cocobacillary forms. Therapy with
ampicillin was initiated.

On the tenth day of hospitalization, a chest roentgenogram
revealed total collapse of the left lung. The patient's mental status
deteriorated as severe hypoxemia and moderate hypercapnia de-
veloped. Despite vigorous chest physiotherapy, postural drainage,
and suctioning, there was no improvement in the patient's clinical status.
Her trachea was intubated with a cuffed endotracheal tube (Portex),
and she underwent flexible bronchoscopy, which revealed mucous
plugging of the left main-stem bronchus. She subsequently required
continued mechanical ventilatory support.

A flexible narrow-bore feeding tube with stylet (NutriFlex) was
passed through her right nostril under manual guidance from the

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FIGURE 1A (top). Feeding tube traversing bronchus intermedius into
right lower lobe, where it enters right pleural space at costophrenic
angle (arrowhead). B (bottom), Feeding tube coiling in right main-
stem bronchus (arrowhead), with tip residing in left main-stem bronchus.