Syndrome of Inappropriate Antidiuretic Hormone Secretion

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The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a clinical syndrome in which enhanced secretion or action of antidiuretic hormone (ADH) due to various disease processes and medications causes persistent hyponatremia and inappropriately elevated urine osmolality. Normally, ADH, or arginine vasopressin, is secreted from the posterior lobe of the pituitary gland in response to a decrease in plasma volume or an increase in serum osmolality. In SIADH, secretion of ADH is not caused by a hemodynamic disturbance and is mediated through nonosmotic receptors, resulting in water retention and dilutional hyponatremia. The incidence of hyponatremia in hospitalized patients is 2.5%, and SIADH is the most common cause of hyponatremia in this population.[1] As early as 1957, Schwartz described SIADH in 2 patients with bronchogenic carcinoma.[2] This article reviews the etiology, pathogenesis, and diagnosis of SIADH. Treatment strategies in various clinical scenarios are also discussed. The workup for potential underlying causes of SIADH is beyond the scope of this article.

TAKE HOME POINTS

- The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common cause of hyponatremia in hospitalized patients.
- Symptoms of SIADH depend on the degree of hyponatremia and the rate at which it develops. Acute decline in serum sodium to below 120 mEq/L can cause life-threatening symptoms, while gradual decline causes nonspecific symptoms.
- SIADH is a diagnosis of exclusion, and adrenal, cardiac, liver, kidney, and thyroid dysfunction must be ruled out.
- Mild asymptomatic hyponatremia (serum sodium > 125 mEq/L) is treated with fluid restriction.
- Severe symptomatic hyponatremia is treated with hypertonic saline in addition to fluid restriction. In treating SIADH, the osmolality of the infused saline must exceed the osmolality of the patient's urine.
- To avoid neurologic complications due to rapid shifts in sodium, the serum sodium level should be raised no faster than 1 to 2 mEq per hour, and no faster than 8 to 12 mEq per day.

PATHOPHYSIOLOGY

ADH is a nonapeptide hormone that is synthesized in the hypothalamus and transported down the pituitary stalk to the posterior pituitary, where it is stored.[3] Increased osmotic pressure caused by increased plasma osmolality is a major stimulus for ADH release, which is mediated through the osmoreceptors in the hypothalamus. Volume depletion is another major stimulus for ADH release, which is mediated through baroreceptors at various sites, including the left atrium, pulmonary veins, carotid sinus, and aortic arch. The antidiuretic action of ADH occurs when the active hormone binds to the V2 receptors on the cells lining the collecting tubules in the kidney, stimulating cyclic adenosine monophosphate and leading to the insertion of aquaporin-2 channels into the apical membrane of the collecting tubule cells. This in turn facilitates transport of solute-free water through the tubular cells, causing water reabsorption in the renal medulla.[3–5] In SIADH, ADH is inappropriately secreted, resulting in unregulated water reabsorption and a measured dilutional hyponatremia.

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Table. Causes of the Syndrome of Inappropriate Antidiuretic Hormone Secretion

Mechanism	Etiology
Increased secretion of ADH	Central nervous system: stroke, hemorrhage, infection, trauma, psychosis Drugs (most common): cyclophosphamide, vincristine, vinblastine, amiodarone, ciprofloxacin, theophylline, antipsychotic drugs (haloperidol, thioridazine, thiothixene), SSRIs, TCAs, MAOIs, bromocriptine, carbamazepine, clofibrate Pulmonary conditions: pneumonia, tuberculosis, acute respiratory failure, asthma, atelectasis Postoperative states: major abdominal or thoracic surgeries
Ectopic secretion of ADH	Lung cancers, tumors of duodenum and pancreas, olfactory neuroblastoma, malignant histiocytosis, mesothelioma, occult tumors
Increased sensitivity to ADH	NSAIDs, cyclophosphamide, tolbutamide, carbamazepine, mizoribine, chlorpropamide
Miscellaneous	Exogenous administration of vasopressin, desmopressin Cachexia, malnutrition AIDS

ADH = antidiuretic hormone; MAOIs = monoamine oxidase inhibitors; NSAIDs = nonsteroidal anti-inflammatory drugs; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.

ETIOLOGY

SIADH usually results from either increased secretion of ADH by the posterior pituitary or ectopic secretion of ADH from another site (**Table**). Causes of excess release of ADH from the pituitary gland include central nervous system disturbances[6–8] and certain drugs.[3,4,8–10] Pulmonary conditions, such as pneumonia, tuberculosis, acute respiratory failure, asthma, and atelectasis, have also been associated with increased production of ADH.[3,5,6,8,11] SIADH is one of the most frequent causes of hyponatremia in hospitalized patients with AIDS, in whom SIADH can be related to adrenal insufficiency or pneumonia.[12] Finally, postoperative states in patients who undergo major abdominal and thoracic surgical procedures as well as chronic pain syndromes can result in increased secretion of ADH; in these scenarios, ADH release is believed to be mediated by pain afferents.[4,5] Ectopic secretion of ADH has been associated with small cell lung cancer, bronchogenic carcinoma, duodenal tumors, pancreatic tumors, thymus tumors, olfactory neuroblastoma, sarcoma, malignant histiocytosis, mesothelioma, and other occult tumors.[1,4,5,6,8,11,13]

Other mechanisms implicated in SIADH include increased sensitivity to ADH in the kidney; reset osmostat, in which ADH release is normally regulated around a lower osmolality set-point, leading to mild asymptomatic hyponatremia (124–134 mEq/L) that fluctuates around the reset level of serum sodium;[14,15] failure to suppress ADH completely at low osmolality (incomplete pituitary stalk section); and exogenous administration. Medications that can increase sensitivity to ADH and result in SIADH include chlorpropamide, tolbutamide, carbamazepine, mizoribine, nonsteroidal anti-inflammatory drugs, and cyclophosphamide.[3,4,8,9] Approximately 30% of patients who underwent transsphenoidal pituitary surgery developed hyponatremia due to inappropriate secretion of ADH from the injured pituitary stalk.[15] Miscellaneous causes of SIADH include cachexia, malnutrition, and administration of desmopressin.[16]

CLINICAL FEATURES

The signs and symptoms of SIADH depend on both the degree of hyponatremia and the rate at which hyponatremia develops. Patients whose sodium concentration has decreased slowly over a long period of time may be completely asymptomatic.[5,11] In these patients, there can be nonspecific symptoms such as anorexia, nausea, vomiting, irritability, headaches, and abdominal cramps.[4] Conversely, patients who have undergone rapid declines in sodium concentration tend to have more symptoms. A serum sodium concentration less than 120 mEq/L or serum osmolality less than 240 mOsm/kg is considered serious, irrespective of the rate of decline. With this degree of hyponatremia, patients can experience cerebral edema, which may manifest as headache, nausea, restlessness, irritability, muscle cramps, generalized weakness, hyporeflexia, confusion, coma, or seizures and can cause permanent brain damage, brainstem herniation, or death.[3,4,8,17]

EVALUATION AND DIAGNOSIS

As SIADH has a varied etiology, a careful history is important and should include comorbidities, current medications, and patients' symptoms. There are no significant findings in the physical examination of a patient with SIADH, although signs of dehydration or edema would make the diagnosis unlikely. Patients with moderate to severe hyponatremia need to be thoroughly assessed to rule out potential complications.

The key points in diagnosing SIADH are the serum sodium concentration, tonicity of plasma and urine, urine sodium concentration, and clinical volume status. Findings of hyponatremia (serum sodium concentration

< 135 mEq/L), hypotonicity (plasma osmolality < 280 mOsm/kg), inappropriately concentrated urine (> 100 mOsm/kg), and an elevated urine sodium concentration (> 20 mEq/L) are consistent with SIADH; however, a low urine sodium concentration (< 20 mEq/L) does not exclude the diagnosis.[4,5,13,17] Patients with SIADH are clinically euvolemic (subclinical plasma volume expansion without clinically significant edema). Hypouricemia occasionally may be associated with SIADH as a result of increased excretion of nitrogen waste and plasma dilution.[16]

Because SIADH is a diagnosis of exclusion, it is necessary to rule out thyroid, adrenal, cardiac, liver, and kidney dysfunction through laboratory testing (thyroid-stimulating hormone level, cortisol stimulation test, brain natriuretic peptide level, liver function tests, serum blood urea nitrogen level, and serum creatinine level).[4,13] Assay of serum ADH level is not mandatory.[6] Common causes of SIADH can be screened for by chest radiograph and computed tomography head scan, if clinically indicated.

Supplemental diagnostic findings that are only of theoretical interest and are not required for the diagnosis of SIADH include an abnormal water load test result (this test is not recommended as it can precipitate severe hyponatremia)[1,8] and inappropriately increased ADH levels relative to plasma osmolality.

SIADH AND CEREBRAL SALT WASTING SYNDROME

Cerebral salt wasting syndrome (CSWS) is a rare syndrome that has been described in patients with cerebral tumors and subarachnoid hemorrhage and in patients who have undergone transsphenoidal pituitary surgery.[17,18] CSWS mimics SIADH (ie, hyponatremia, increased urine osmolarity, urine sodium > 20 mEq/L, and urine osmolality > serum osmolality), but in fact represents appropriate water resorption in the face of a salt wasting and a secondarily hypovolemic state.[19] These patients may also have hypouricemia due to increased urinary uric acid excretion.[20] The etiology of CSWS is unclear.[21,22]

Fluid restriction may help differentiate SIADH from CSWS, as restriction will correct the hypouricemia and increased fractional excretion of urate in patients with SIADH, whereas in patients with CSWS both will persist after fluid restriction.[20] The treatment of CSWS differs from that of SIADH. Infusion of isotonic saline to correct the volume depletion is usually effective in reversing the hyponatremia in CSWS since euvolemia will suppress ADH secretion.[23] Some patients may benefit from fludrocortisone therapy.[18]

TREATMENT

Treatment of SIADH depends on the symptoms, serum sodium concentration, rapidity of onset of hyponatremia, and primary etiology. Although treating the underlying etiology is essential to the resolution of SIADH, doing so is often difficult due to noncompliance. Fluid restriction is the first-line treatment in mild asymptomatic hyponatremia (serum sodium concentration > 125 mEq/L), which generally improves with correction of the underlying cause and restriction of free fluid intake to between 800 and 1000 mL/day. If there is no response, fluid intake can be restricted to 500 to 600 mL/day, but compliance is very difficult.[3,5] To enhance compliance, patients must be educated that a regular diet contains 700 to 1000 mL of water even before accounting for free water intake.

In mild symptomatic hyponatremia, a loop diuretic (not thiazides) can be added to fluid restriction. Loop diuretics interfere with the action of ADH in the collecting tubule by inhibiting free water reabsorption, eventually achieving a negative water balance. Careful attention must be given when using loop diuretics to prevent depletion of other electrolytes.

If saline is used to treat hyponatremia in SIADH, the osmolality of the infused saline generally must exceed the osmolality of the patient's urine. Therefore, infusion of isotonic saline (osmolality of 308 mOsm/L) is not recommended in patients with SIADH whose urine osmolality exceeds 308 mOsm/L because it may actually worsen their hyponatremia.[24] In such cases, the kidney excretes the solute from normal saline in concentrated urine, while the unexcreted volume is retained as free water, resulting in a net fluid gain and exacerbation of the hyponatremia.[3,5] However, one study demonstrated that isotonic saline improved the serum sodium level in water-restricted SIADH patients as long as the sodium and potassium concentration of the urine did not exceed the sodium concentration of the infused isotonic saline (ie, 154 mEq/ L).[25]

Symptomatic patients with severe hyponatremia (serum sodium concentration < 125 mEq/L) may require hypertonic saline in addition to fluid restriction.[5] Hypertonic saline can be infused via a pump with careful monitoring, and urine osmolality can be followed to guide therapy. As a rule of thumb, hypertonic saline can be switched to isotonic saline when the urine osmolality is less than 300 mOsm/L. Caution must be taken in correcting hyponatremia, as aggressive and overly rapid correction may induce central pontine myelinosis, a demyelinating condition that affects the pontine and extrapontine neurons, leading

to quadriplegia, pseudobulbar palsy, seizures, coma, or even death.[5,7,26,27] Patients at high risk for central pontine myelinosis include those with hypokalemia or burns, patients on thiazide diuretics, alcoholics, and the elderly. To avoid this serious consequence, the serum sodium level should be raised at a rate no faster than 1 to 2 mEq per hour, and the rate should not exceed 8 to 12 mEq per day. Once the serum sodium rises above 125 mEq/L, the risk of seizure and death is reduced and the daily correction should be slowed to 5 to 6 mEq per day.[5]

Patients with chronic SIADH (ie, those with reset osmostat syndrome or cancer) may benefit from a high-sodium diet combined with loop diuretics. In most instances where SIADH is induced by medications, resectable tumors, or lung pathologies, serum sodium normalizes after removal of the offending agent. In patients with severe SIADH due to unresectable tumors or in chronic states of any kind, demeclocycline 600 to 1200 mg daily in divided doses can be used.[8,28] This agent improves SIADH by interfering with the kidney's response to ADH at the collecting tubule. Although expensive, it is well tolerated. Other agents that can be used in long-term management include urea and diuretics.[5,14,24] Lithium should be avoided because it potentiates the central nervous system side effects of hyponatremia.[28]

Recently, the vasopressin receptor antagonist conivaptan was approved for the treatment of dilutional hyponatremia (SIADH).[29,30] Conivaptan causes loss of body water without loss of electrolytes. It is given intravenously. Several other vasopressin receptor antagonists are being evaluated in clinical trials.[31]

Chronic, asymptomatic, mild to moderate hyponatremia where the cause is known but not easily or quickly reversed may be managed without fluid restriction or medications. Patients with stable, chronic sodium levels above 125 mEq/L who are asymptomatic may not derive much benefit from treatment considering the expense of demeclocycline and the discomfort of severe water restriction.

CONCLUSION

SIADH is one of the most common causes of hyponatremia and should be considered in hyponatremic patients. Careful history including comorbidities, medications, and symptoms and a thorough physical examination are essential for an accurate diagnosis. As a diagnosis of exclusion, appropriate tests must be done to rule out other potential causes of hyponatremia. Early diagnosis and appropriate treatment will prevent serious complications of this common disorder. **HP**

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