Review Article

Syndrome of inappropriate antidiuretic hormone secretion: Revisiting a classical endocrine disorder

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ABSTRACT

Hyponatremia occurs in about 30% of hospitalized patients and syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a common cause of hyponatremia. SIADH should be differentiated from other causes of hyponatremia like diuretic therapy, hypothyroidism and hypocortisolism. Where possible, all attempts should be made to identify and rectify the cause of SIADH. The main problem in SIADH is fluid excess, and hyponatremia is dilutional in nature. Fluid restriction is the main stay in the treatment of SIADH; however, cerebral salt wasting should be excluded in the clinical setting of brain surgeries, subarachnoid hemorrhage, etc. Fluid restriction in cerebral salt wasting can be hazardous. Sodium correction in chronic hyponatremia (onset >48 hours) should be done slowly to avoid deleterious effects in brain.

Key words: Hyponatremia, syndrome of inappropriate antidiuretic hormone secretion, cerebral salt wasting

Introduction

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) was initially described by Leaf and Mamby.[1] SIADH consists of hyponatremia, inappropriately elevated urine osmolality, excessive urine sodium and decreased serum osmolality in a euvolemic patient without edema. These findings should occur in the absence of diuretic treatment with normal cardiac, renal, adrenal, hepatic and thyroid function. Hyponatremia occurs in about 30% of hospitalized patients[2] and SIADH is the most frequent cause of hyponatremia. The main issue in SIADH is excess water and hyponatremia is dilutional in nature. The treating physician should address the excess water rather than concentrating on sodium levels alone.

During stressful situations, increased secretion of several hormones including steroids, catecholamines, growth hormone, prolactin and vasopressin occurs. Vasopressin is released from paraventricular nucleus of hypothalamus, together with corticotropin releasing hormone (CRH).

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Role of Limbic System in Sodium and Water Balance

The limbic system consists of hippocampus, amygdala, anterior thalamic nuclei, septum, limbic cortex and fornix. It is an interconnected complex and its control center is hypothalamus. Limbic system controls behavior as well as many internal functions including osmolality of body fluids. Supraoptic and paraventricular nuclei in hypothalamus synthesize ADH, and axons from these nuclei extend through the pituitary stalk to the posterior pituitary.

During resting states, ADH is stored in posterior pituitary. The osmoreceptors located near supraoptic nuclei of hypothalamus create a feedback control system for ADH secretion. These osmoreceptors respond to change in the extracellular fluid (ECF) osmolality which results from changes in serum sodium concentration. In hyperosmolar states, osmoreceptor cells shrink which stimulates secretion of ADH. On the contrary, in hypo-osmolar

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states, osmoreceptors swell up which causes decreased production of ADH.

In addition, the stretch receptors located in left atrium and the baroreceptors situated in the aortic area and carotid sinus work as sensors which sense changes in effective circulating blood volume and blood pressure. These receptors provide information to hypothalamus via ascending neural fibers. Inhibitory or facilitatory impulses from the hypothalamus to the pituitary can then be initiated which decrease or increase the excretion rate of ADH, respectively. Limbic system activation by stimuli like pain, nausea, fear, major trauma and surgery leads to increase in ADH production.

Etiology

SIADH can be secondary to a variety of problems ranging from drugs to malignancies. Sometimes, it may be multifactorial. A search for secondary causes is often rewarding and must be done wherever possible.

Drugs

A number of drugs can enhance ADH release or action. Table 1 lists the drugs which can contribute to the development of SIADH.[3-11]

Central nervous system disturbances

Many central nervous system (CNS) disorders are associated with SIADH. Disorders like stroke, infection, trauma, hemorrhage and psychosis enhance ADH release. However, hyponatremia associated with severe neurological events including intracerebral bleeding may also be due to cerebral salt wasting (CSW).

Malignancies

Lung tumors, especially small cell carcinoma, produce ADH ectopically.[12] Other tumors like cancers of pancreas, duodenum, head and neck may also produce ADH occasionally.[13,14] Also, many drugs used in the cancer treatment can cause SIADH as discussed earlier [Table 1].

Table 1: Drugs commonly associated with development of syndrome of inappropriate antidiuretic hormone secretion

Cabamazeine	Mono Amino Oxidase inhibitors
Oxcarbamazepine	Melphalan
Chlorpropamide	Imatinib
Cyclophosphamide	Methotrexate
Sodium valproate	Ifosfamide
Vincristine	Opiates
Vinorelbin	Non steroidal anti-inflammatory drugs (NSAIDs)
Amiodarone	
Ciprofloxacin	
Vinblastine	Interferon-alpha
Cisplatin	Interferon-gamma
Thiothixene	Bromocriptine
Haloperidol	Amphetamines
Amitriptyline	Selective serotonin reuptake inhibitors (SSRIs)

Pulmonary disease

Several lung disorders including pneumonia can cause SIADH by unknown mechanisms.[15] Other pulmonary diseases causing SIADH are bronchial asthma, atelectasis, acute respiratory failure and pneumothorax.

Surgery

Major surgical procedures, which include abdominal and thoracic surgeries, can cause hypersecretion of ADH, probably mediated by pain afferents.[16,17] Pituitary surgery is also associated with inappropriate ADH release. However, the hyponatremia following pituitary surgery can also be due to cortisol deficiency and CSW. It is important to distinguish between SIADH and CSW, as the line of management is different. Patients with CSW are usually volume depleted and further fluid restriction in CSW can lead to dangerous consequences.

Hormone administration

Use of vasopressin, desmopressin or oxytocin can cause SIADH by increasing the activity of vasopressor-2 (V2) vasopressin receptor.[18,19]

Hereditary syndrome of inappropriate antidiuretic hormone secretion

Two genetic syndromes, one affecting the gene for renal V2 receptor and the other affecting osmolality sensing in hypothalamus, have been identified. The former is called nephrogenic syndrome and the latter is termed as hypothalamic syndrome.

In the nephrogenic syndrome, a gain-of-function mutation in the gene for V2 receptor, which is located on the X chromosome, has been identified[20] V2 vasopressor receptor is responsible for water reabsorption in the renal collecting duct. Gain-of-function mutation in the gene for V2 receptor results in persistent activation of receptor.

In the hypothalamic syndrome, mutation in the transient receptor potential vanilloid type 4 (*TRPV4*) gene has been identified.[21] Central osmolality sensing mechanism in hypothalamus is encoded by *TRPV4* gene. Loss of function nonsynonymous polymorphism in this gene affects the sensing of hypo-osmolality. This interferes with appropriate suppression of ADH release in the presence of hypo-osmolality.

HIV infection

Both HIV infection and acquired immune deficiency

syndrome (AIDS) are associated with SIADH. Adrenal insufficiency, opportunistic infections and malignant diseases associated with HIV infection may also contribute to the development of hyponatremia.[22]

Idiopathic

Idiopathic SIADH can be due to occult tumors or temporal arteritis.[23,24]

Pathophysiology

Certain basic principles of fluid and electrolyte balance need to be kept in mind when analyzing a case of hyponatremia. (a) Water moves freely across cell membranes. Two-thirds of total body water is intracellular and one-third is extracellular. (b) Sodium is the predominantly extracellular osmotically active particle and sodium concentration is an indication of intracellular volume. This has to do with the fact that the intracellular active particles, which mainly include potassium salts of macromolecular ions, are mostly constant and any change in these ion concentrations takes days (>48 hours) to manifest. When the sodium concentration in the (ECF) changes, it is the water which moves across membranes to maintain stable osmolality across the two compartments. Hence, irrespective of the etiology, hyponatremia indicates swollen cells. (c) Even a transient ECF expansion results in natriuresis. This is initiated by downregulation of Na channels in the proximal tubules of the kidneys.

Hyponatremia in SIADH is a result of excess water and is not primarily due to serum sodium deficiency. It is the combination of water retention together with secondary solute loss, which results in reduction in serum sodium.[25]

Hyponatremia is mediated initially by ADH-induced water retention that results in volume expansion which activities secondary natriuretic mechanisms causing sodium and water loss and restoration of euvolemia. This euvolemia should not be confused with normal water content of the body. This indicates that the ECF volume is normal/near normal, but the intracellular fluid (ICF) volume is expanded. The dynamic nature of the natriuresis in the acute states creates problems in management.

The role of natriuretic peptides in patients with SIADH has been a topic of discussion, and at least in a selected group of patients the natiuretic peptides do seem to play a role, albeit minor, when compared to their dominant role in CSW.[26,27] As there is no impairment of volume regulatory hormones such as aldosterone, patients with SIADH are euvolemic, unless there exists a second problem like vomiting, diarrhea or diuretic therapy. However, the clinical assessment of volume status is often inaccurate when done even by experienced physicians. In chronic hyponatremia, the water retention and sodium loss are well balanced and the serum Na is usually stable. There are several clinical conditions, which manifest as hyponatremia, and SIADH should be differentiated from such disorders. Table 2 enlists few of these conditions.

Pseudohyponatremia

Pseudohyponatremia is associated with normal serum osmolality. Fats and proteins account for 7% of plasma volume and the remaining 93% is made up of plasma water. In conditions associated with marked hyperlipidemia and hyperproteinemia, plasma water fraction can fall below 80% and rest of the plasma volume is made up by fat/protein. In these situations, the measured sodium concentration in total plasma volume will be reduced as it contains less plasma water. In fact, the plasma water as such will have normal sodium content and normal osmolality.

Hyponatremia associated with hyperglycemia

Serum glucose levels must be monitored to rule out hyperglycemia, which results in decrease in the measured serum sodium levels as the osmotic effect of glucose draws water into the intravascular space.

Diagnosis

Bartter and Schwartz criteria for SIADH:

1. Decreased plasma osmolality (<275 mosm/kg)
2. Inappropriately concentrated urine (>100 mosm/kg)
3. Euvolemic
4. Elevated urine Na (>20 mEq/L)
5. Euthyroid, eucortisolemic and no diuretic use.

Chest X-ray and in selected cases, computed tomography (CT) scan of head may be appropriate to reveal an underlying cause.

Table 2: Differential diagnosis of syndrome of inappropriate antidiuretic hormone secretion

Cerebral salt wasting
Hypothyroidism
Hyperglycemia
Adrenal insufficiency
Hypopituitarism
Psychogenic polydipsia
Walderstorm's hypergammaglobulinemia
Pseudohyponatremia
Hyperlipidemia
Hyperproteinemia

Treatment

General principles

The following approach is suggested:

1. Identify whether the hyponatremia is acute or chronic. 48 hours is generally taken as the cutoff point. This is the time that the brain cells take to generate osmotically active particles in response to the cellular swelling. As a general rule, if the patient is completely asymptomatic, the hyponatremia is most likely a chronic one.
2. If clearly known to be acute, correction can be fast. The source of retained effective water has to be identified and stopped. If possible, the underlying cause should be treated. A thorough search should be done to identify the underlying cause and a detailed history must be obtained from patient and/or caregivers regarding onset and duration of neurological symptoms, drugs, etc. Reviewing the medication chart and drugs prior to admission is worthwhile and is often rewarding. Dextrose based intravenous fluids which are commonly used in postoperative setting can result in hyponatremia.
3. Treatment of chronic hyponatremia varies from that of acute hyponatremia. Hyponatremia correction should be done cautiously to avoid the risk of inducing osmotic central pontine myelinolysis especially in chronic hyponatremia. There are various recommendations for the correction limit/day for chronic hyponatremia, varying from 8 to 12 meq/day. However, most literature suggests that the lower limit of this range which is 8 meq/day should be the aim to avoid osmotic demyelination. Aggressive management is indicated in patients with severe symptoms like seizures or altered mental changes and those with extremely low levels of sodium (less than 120 meq/L). This should be done at the rate of around 5meq/L over few hours. However, the total limit for the day should be around 8 meq/ L.

There are two formulas which are commonly used for calculating the deficit, and there are few issues associated with using these formulas, which should be taken into account:

1. Na deficit = 0.6 × body wt × (normal Na − current Na). What are the problems associated with this formula? It assumes constant total body water and also fails to take into account the volume of fluid infused. SIADH is associated with water retention, and hence the total body water is higher in the hyponatremic state. Secondly, it assumes a closed system. We have to make assumptions about the amount of Na excreted and this has to be added to the deficit to determine the amount to be infused in 24 hours. This is especially problematic in acute hyponatremia when there may be significant alterations due to the sodium loss in the urine.
2. Change is serum Na expected with infusion of 1 L of infusate = (Na concentration of infusate – current serum Na)/(Total Body Water + 1).
   This formula is better in that the infusate volume is taken into account. Again, it fails to take into account the increase in ICF in the hyponatremic state. The above-mentioned fallacies explain the unsatisfactory results obtained sometimes on using these formulae. Treatment should be tailored on individual basis and these formulas should only act as rough guides.

Alternate approaches based on the principles of tonicity balance are available. This can be a bit laborious at times, but probably is worth mentioning. The principles are outlined[28] here briefly.

1. The number of osmotically active particles in the ICF is relatively constant. This is calculated by two-thirds of total body water × 140. This, divided by the current low serum Na, gives the current ICF volume. This allows calculation of the fluid that has to be lost by water restriction.
2. The Na deficit has to be calculated separately. TBW × 1/3 × 140 gives the normal Na content of the ECF. This, divided by the current Na, gives the amount of Na to be given to correct the ECF deficit.
3. Always consider the urine Na concentration. Use a fluid with concentration of Na above that in the urine to bring up the Na levels.

There are several online calculators [Table 3] available to help physicians with the sodium correction in hyponatremia. Again, these should be used only as guides. It must be remembered that each patient is unique and an individualized treatment plan is often needed.

Fluid restriction

Fluid restriction is the main stay of treatment, especially in SIADH. Fluid restriction to less than the urine output is the primary therapy in hyponatremia. Usual recommended fluid intake is less than 800 mg/day. In the setting where hyponatremia is associated with head trauma, subarachnoid hemorrhage, etc., CSW should be ruled out as a cause of hyponatremia prior to recommending fluid restriction. These patients are usually volume depleted and further fluid restriction can be dangerous to the patient.

Table 3: References for online calculators for hyponatremia correction

http://www.nephromatic.com/sodium_correction.php
http://www.medcalc.com/sodium.html
http://www.globalrph.com/custom_saline.htm

Intravenous saline

It should be noted that aldosterone is unaffected in SIADH and the sodium balance will be usually normal. If isotonic saline is administered, the water will be retained and sodium will be excreted in urine, leading to possible worsening of hyponatremia. Hence, isotonic saline is not usually effective in raising serum sodium in SIADH. Hypertonic saline raises serum sodium, but the response will partially dissipate over time.

Oral salt tablets with loop diuretics

The effect of salt tablets can be enhanced by administration of a loop diuretic like furosemide which interferes with the countercurrent concentrating mechanism by decreasing sodium chloride reabsorption in the thick ascending limb of loop of Henle. This results in excretion of isotonic urine and considerable fluid loss. The usual dose is 9 g salt daily with 20 mg oral furosemide twice a day. Furosemide is particularly useful in the setting where the urine osmolality is more than 500 mosm/L or if the urine osmolality is more than double of serum osmolality.

Urea

Urea, at a dose of 30 g/day, increases urinary solute excretion and enhances water excretion.[29,30]

Vasopressin receptor antagonists

Vasopressin or ADH has three receptors, V1a, V1b and V2 receptors. Antidiuretic response is mediated by V2 receptor, while V1a and V1b receptors cause vasoconstriction and adrenocortcotropic hormone (ACTH) hormone release. Vasopressin receptor antagonists produce a selective water diuresis without interfering with sodium and potassium excretion.[31,32]

Tolvaptan, satavaptan and lixivaptan are selective V2 receptor antagonists, while conivaptan blocks both V1 and V1a receptors. In a randomized controlled trial, intravenous conivaptan significantly raised serum sodium concentration.[33] In a placebo-controlled, randomized, double-blind study, oral conivaptan 40 and 80 mg/day was well tolerated and efficacious in correcting serum sodium in hyponatremia.[34]

The use of V2 receptor antagonists is limited due to increased thirst,[35] rapid correction of hyponatremia as demonstrated in SALT trials and the high cost. Vasopressin receptor antagonists should not be used in hyponatremic patients who are volume depleted.

Demeclocycline

It is a tetracycline derivative which induces drug-induced diabetes insipidus by acting on the collecting tubule cell to diminish its responsiveness to ADH.[36] The role is limited in emergency care due to the slow onset of action.

Rate of correction

Rapid correction of hyponatremia can lead to central pontine myelinolysis. The risk is highest in premenopausal women.[37] The risk of central pontine myelinolysis is lesser in patients with hyperacute hyponatremia that develops rapidly over few hours due to marked increase in water intake, for example, marathon runners, methamphetamine users, etc. Osmotic demyelination occurs in patients in whom the serum sodium concentration increases to more than 12 meq/L in the first 24 hours.[38] The goals of therapy are to raise the serum sodium concentration by less than 10 meq/L in the first 24 hours and by less than 18 meq/L in the first 48 hours.[31,39]

Osmotic demyelination syndrome

Osmotic demyelination syndrome (ODS) occurs with rapid correction of severe hyponatremia. There are several risk factors for ODS which include serum sodium concentration at presentation, duration of hyponatremia and rapid rate of correction, alcoholism, malnutrition, liver disease and hypokalemia. Most of the ODS occurs in patients who present with a serum sodium concentration of 105 meq/L or less[31,38] and ODS rarely happens to a patient who presents with an initial sodium of less than 120 meq/L except in patients with desmopressin-induced hyponatremia[40] or in the setting of liver transplantation.[41]

Clinical features can be delayed by a few days after rapid sodium correction. Symptoms include neurological manifestations like dysarthria, dysphagia, paraparesis, quadriparesis, confusion, coma, etc. Seizures are very rare. Locked-in syndrome can occur when there is bilateral pontine demyelination. ODS can be detected by magnetic resonance imaging (MRI) scan, but it may take up to 4 weeks to become positive. Hence, a negative study earlier in the course does not rule out ODS.

Treatment is often difficult; importance should be given to prevention. As previously discussed, slow correction of hyponatremia is essential in the prevention of ODS. Minocycline[42,43] has been shown to be efficacious in preventing ODS if concurrently administered with hypertonic saline or if initiated within 24 hours of correction of hyponatremia. ODS is associated with poor prognosis. Few case reports suggest benefit from early relowering of serum sodium. Supportive treatment to prevent aspiration pneumonia and ventilatory care are needed. Plasmapheresis[44] may also be beneficial.

Special situations

Cerebral salt wasting

CSW is a distinct disease which occurs in the setting of CNS disorders which manifest with hyponatremia. It was originally described by Peters *et al*.,[45] in 1950. However, some authorities argue that such a condition does not exist and CSW is a misnomer.[46]

CSW is not as common as SIADH. CSW should be suspected in hypovolemic patients with hyponatremia in the setting of CNS disorders. There are case reports of CSW occurring in the presence of pituitary adenoma[47] Distinction from SIADH is often difficult, but essential as the treatment is different in both the conditions. Fluid restriction is the primary therapy in SIADH, but in CSW, fluid restriction may increase the risk of cerebral infarction. Both the disorders share few features like inappropriately high urine osmolality in the presence of hyponatremia, high urine sodium (often more than 40 meq/L) and reduced serum uric acid concentration.

The presence of volume depletion, which is manifested as reduced skin turgor, hypotension, elevated hematocrit and increased blood urea nitrogen (BUN)/serum creatinine ratio, favors diagnosis of CSW.[46,48] Isotonic saline is used for volume repletion in CSW. Salt tablets can be administered once the patient can tolerate oral medications. It is common to use fludrocortisone, a mineralocorticoid in neurosurgical practice, which is found to be useful in CSW.[49] CSW is often transient and long-term treatment is not necessary.

Diagnosing syndrome of inappropriate antidiuretic hormone secretion in patients on diuretics

Many of the sick, hospitalized patients are on diuretics, and diagnosing SIADH is difficult in these situations. Urine sodium and fractional excretion of sodium (FE-Na) are of little use in this setting to differentiate between SIADH and hyponatremia due to diuretic use. Wiebke *et al*.,[50] in their study, found that fractional excretion of uric acid (FE-UA) is very useful in the diagnosis of SIADH in patients who are on diuretics. An FE-UA of 8% had a sensitivity and negative predictive value of 100% in diagnosing SIADH.

Increasing age- A risk factor for syndrome of inappropriate antidiuretic hormone secretion

Advancing age itself may be a risk factor for SIADH due to the normal aging process that affects fluid balance. Normal physiologic changes associated with aging such as elevated ADH and atrial natriuretic hormone levels as well as an increased responsiveness to osmotic stimulation predisposes elderly patients to SIADH.[51,52] Elderly patients also receive many drugs that can cause SIADH and they are at higher risk of developing drug-induced SIADH compared to younger patients.

Postoperative risk of hyponatremia

There are several factors associated with the occurrence of hyponatremia in the postoperative period. Postoperative patients are often infused with hypotonic solutions like 5% dextrose in water, which cause dilution of plasma electrolyte concentration and predispose to hyponatremia. Patients who are on mechanical ventilation and/or positive pressure breathing devices after surgeries may develop SIADH due to decreased production of atrial natriuretic peptide (ANP) which stimulates ADH secretion. Besides, stress, hypotension, pain, general anesthesia and medications used after surgery like opioids may precipitate the development of SIADH.

Conclusion

Hyponatremia is commonly encountered in inpatient settings and rarely encountered in outpatient clinics. SIADH is a common cause of hyponatremia. An active search for the cause of SIADH should be done and offending cause should be treated whenever possible. Treatment is mainly fluid restriction. However, in CNS disorders associated with hyponatremia, CSW should be ruled out, as the treatment modalities are different. ODS is a serious, but rare complication of treatment of hyponatremia. Sodium correction should be done gradually in chronic hyponatremia. There are several other causes of hyponatremia, including hypothyroidism and hypoadrenalism, and these disorders should be ruled out prior to diagnosing as SIADH. FE-UA is a good tool in diagnosing SIADH in patients who are on diuretics.

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Announcement

Nominations are invited for the Orations of the Endocrine Society of India from members of the Endocrine Society of India. MMS Ahuja Oration, Subhash Mukherjee Oration and PN Shah Memorial Orations. The nomination for these orations must include full details of the member his/hr brief bio-data, list of the publication, reprints of three of his/her peer reviewed publications, and brief summary of the proposed topic for the oration. (in quadruplicate). Completed Nominations may be sent to the Secretary, Endocrine Society of India, Prof. Rakesh Sahay, Department of Endocrinology, Osmania General Hospital, 2rd Floor, Golden Jubilee Block, Osmania General Hospital, Afzalgunj, Hyderabad 500012. A soft copy of the same may be also be sent by email to indianendosociety@gmail.com, with a copy marked to Chairman, Credential Committee, Prof. RV Jayakumar, (rvjayakumar@amrita.aims.edu). The last date for receipt of the nominations is 30 June 2011. Further details can be obtained from the website www.endosocietyindia.org