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RESEARCH ARTICLE

SYNDROME OF INAPPROPRIATE ANTIDIURESIS -AN OVERVIEW

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ABSTRACT

Hyponatremia is the most common electrolyte imbalance noted in routine clinical practice, which is defined by a blood sodium level below 135 mEq/l. Syndrome of inappropriate antidiuresisis the most common cause of hyponatremia in hospitalized patients. We in our article, review the physiology, pathophysiology, etiology, presentations, evaluation and treatment of SIAD.

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INTRODUCTION

Syndrome of inappropriate antidiuretic hormone secretion[SIADH] is also known as Syndrome of antidiuresis[SIAD]. In recent years the interest and knowledge of this clinical entity have considerably advanced, so much to justify a change in its traditional title, from SIADH to SIAD, as all affected patients will not have an increasingly circulating ADH levels, resulting from increased release by the pituitary gland or ectopic production. William Schwartz and Frederic Bartter in 1967 discovered SIAD in two patients with lung malignancy. They created the classic Schwartz and Bartter criteria for SIAD diagnosis. Impaired water excretion, which in turn causes hyponatremia with hypervolemia or euvolemia, as a hallmark of SIAD.
[1-3]

PHYSIOLOGY OF AVP [ARGININE VASOPRESSIN]

AVP is a nonapeptide with configurational similarities to oxytocin. The precursor protein of AVP vasopressin-neurophysin 2-copeptin preprotein, which traverse via the supraoptic-hypophyseal tract into the posterior pituitary, is produced in the cell bodies of neurons in the supraoptic and paraventricular nuclei of the anterior hypothalamus. In the terminal dilatations of secretory neurons present next to arteries, the preprotein is broken there into AVP, neurophysin 2, and copeptin, then preserved in secretory granules along with a carrier protein, neurophysin. Effective circulation volume depletion and hyperosmolality, which are detected by the baroreceptors and osmoreceptors respectively, are the prime triggers for AVP secretion.

The hypothalamus contains a specialized type of cells called osmoreceptors which detect changes in the osmolality of extracellular fluid (ECF). Baroreceptors are found in the carotid sinus, aortic arch, and left atrium. By responding to a change in effective circulating volume, these receptors take part in the non-osmolar control of AVP release. V1a, V1b (also known as V3), and V2 are the three main receptors that are responsible for the binding of AVP to the cell membrane of target tissues and mediate its various actions. The volume receptors and osmoreceptors work closely to promote or reduce AVP release in the majority of physiological conditions. However, when the extracellular osmolality is normal or lowered, a decrease in actual or effective circulation volume acts as a more powerful stimulant for AVP production. Different medicines and stressful events like pain or anxiety are also responsible for its release. AVP has a half-life of 15-20 minutes, and it is metabolized quickly in the liver and kidneys [FIGURE 1]

PATHOPHYSIOLOGY

Hyponatremia, inappropriately raised urine osmolality (>100 mOsm/kg), and reduced serum osmolality in a patient with euvolemia are the three main components of SIAD. When these symptoms appear along with otherwise normal cardiac, renal, adrenal, hepatic,thyroid function, in the absence of diuretic therapy, and ADH secretion is also stimulated by other conditions such as hypotension, excessive pain, nausea, and stress, when these are absent, SIAD should be diagnosed. In general, plasma sodium concentration is the main osmotic factor affecting the AVP release. In SIAD, patients'

secretion of AVP is inappropriate and non-physiological, which causes increased water reabsorption and dilutional hyponatremia. Natriuresis result from the secretion of natriuretic peptides and the activation of volume receptors. A steady state is eventually reached where sodium intake and excretion are matched. Water consumption plays a crucial role for the syndrome's emergence. If water intake is significantly reduced hyponatremia does not develop, regardless of the cause. People who have this syndrome may also secrete inappropriate amounts of AVP and also experience inappropriate thirst, which causes them to drink excess water than they normally would and cause more water to be excreted, this excessive water consumption is conferred with sustaining hyponatremia.

TYPES OF SIAD

- **Type A-** Occurs independently of plasma osmolality, there is a high level of ADH and urine osmolality.
- **Type B-** Is characterized by a constant release of ADH.
- **Type C-** Is characterized by a baseline plasma sodium concentration that is stable, but lower than normal.
- **Type D-** Shows normal ADH levels but high urine osmolality.

Neurologic manifestations

- Neurologic complications occur corresponding to the brain's response to changes in osmolality. Hyponatremia and hypo-osmolality lead to acute edema of the brain cells.
- Beyond a certain point, the rigid calvaria prevents expansion of brain volume, brain cells have to adapt to persistent hypo-osmolality from that point. Although, a sharp increase in brain water content of more than 5-10% causes severe cerebral edema and herniation which is fatal.
- ECF from the brain moves into the CSF, in response to the decrease in osmolality. To prevent excessive swelling of brain cells potassium and intracellular organic osmolytes (amino acids, glutamate, glutamine, taurine, polyhydric alcohol, myoinositol, methylamine, and creatinine) are lost simultaneously.
- The adaptive process does not match the extrusion kinetics after the correction of hyponatremia, there is rapid reaccumulation of electrolytes in the brain ECF within 24 hours, leading to a notable rise in normal brain contents within the first 48 hours after correction.
- Organic osmolytes then return to normal brain content slowly over 5-7 days. By the fifth day of correction, electrolyte levels in brain contents also return to a normal level along with organic osmolytes. In patients with severe hyponatremia, Irreversible neurologic damage and death may occur when the rate of correction of Na exceeds 0.5 mEq/L/h. when hyponatremia is corrected rapidly osmolytes that were lost in the prevention of brain edema during the development of hyponatremia cannot be restored as quickly.
- Thus, the brain cells are subjected to osmotic injury, develop a devastating condition termed osmotic demyelination. Hypokalemia, advanced liver disease, and severe malnutrition are predisposing factors for the same.

ETIOLOGY: Causes of SIAD are categorized into four main groups

- **Nervous system disorders:** Central nervous system abnormality can increase ADH release from the pituitary gland. These disorders comprise of stroke, hemorrhage, infection, trauma, mental illness, and psychosis.
- **Neoplasticdisorders:** Lung carcinoma and mesothelioma, Carcinomas of the gastrointestinal system, Adrenocortical carcinoma; carcinomas of the genitourinary system, Ewing sarcoma, leukemia, lymphoma, nasopharyngeal carcinoma, neuroblastoma (olfactory), and thymoma.
- **Pulmonary disorders:**pulmonary diseases particularly pneumonia (viral, bacterial, tuberculous), can lead to SIAD by unknown mechanisms, a similar response has infrequently been seen in patients with asthma, atelectasis, acute respiratory failure, and pneumothorax.
- **Drugs causing SIAD:** Several drugs associated with SIAD act by increasing the release or effect of ADH, the most common drugs include carbamazepine, oxcarbazepine, chlorpropamide, cyclophosphamide, and selective serotonin reuptake inhibitors. Carbamazepine and oxcarbazepine act in part by enhancing the sensitivity to ADH. Chlorpropamide enhances the count of V2 receptors at the collecting tubules. As high-dose IV cyclophosphamide is administered with a fluid load to prevent hemorrhagic cystitis, in these patients SIAD is a particular problem, leading to potentially fatal hyponatremia.
- **Miscellaneous causes:** Giant cell arteritis, HIV infection (a common laboratory manifestation seen in HIV infection) either with the acquired immune deficiency syndrome (AIDS) or early symptomatic HIV infection is hyponatremia, it can be due to SIAD, or it can be due to volume depletion, secondary to adrenal insufficiency or gastrointestinal losses. Pneumonia, due to Pneumocystis carinii or other organisms and CNS infections by opportunistic pathogens, is also responsible for SIAD. [4]

PRESENTATION

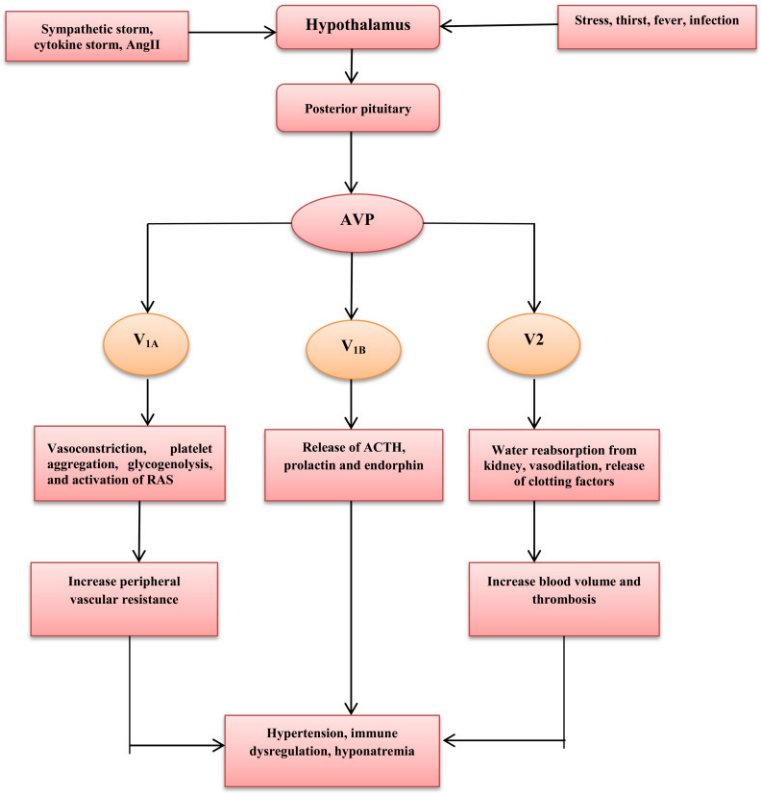
- Symptoms depend on severity and rate of development of hyponatremia.Subsequently, laboratory parameters are used to identify the SIAD. A rapid reduction in serum sodium levels is generally associated with more symptoms than gradual progress towards hyponatremia.
- Cognitive slowness, ataxia, and impaired reaction time, which can lead to recurrent falls are observed in patients with moderate, persistent hyponatremia.
- The severity or acuity of hyponatremia may not be precisely correlated with the signs and symptoms of the condition, some people who are having profound hyponatremia may not exhibit many symptoms according to the severity.
- Initially, anorexia, nausea, and malaise can be seenwhen the serum sodium level is less than 125 mEq/L. Seizures, coma, weakness, headaches, cramps, irritability, drowsiness, and disorientation may result in a further drop in the serum sodium level, cerebral edema and increased intracranial pressure brought on by osmotic fluid are the important factors leading to the above findings.
- It is critical to identify if the patient consumed excessive fluid due to increased thirst, psychogenic polydipsia, or the administration of hypotonic fluids while under medical care. By the history chronicity of the problem may be known, which may have an impact on how rapidly the hyponatremia is corrected.
- Only in severe or rapid-onset hyponatremia can prominent physical examination findings be observed.
- Euvolemia is often indicated by moist mucous membranes without jugular venous pulsation or edema. Comprehensive neurological and chest examinations are required.

EVALUATION

The Schwartz and Bartter Clinical Criterion:

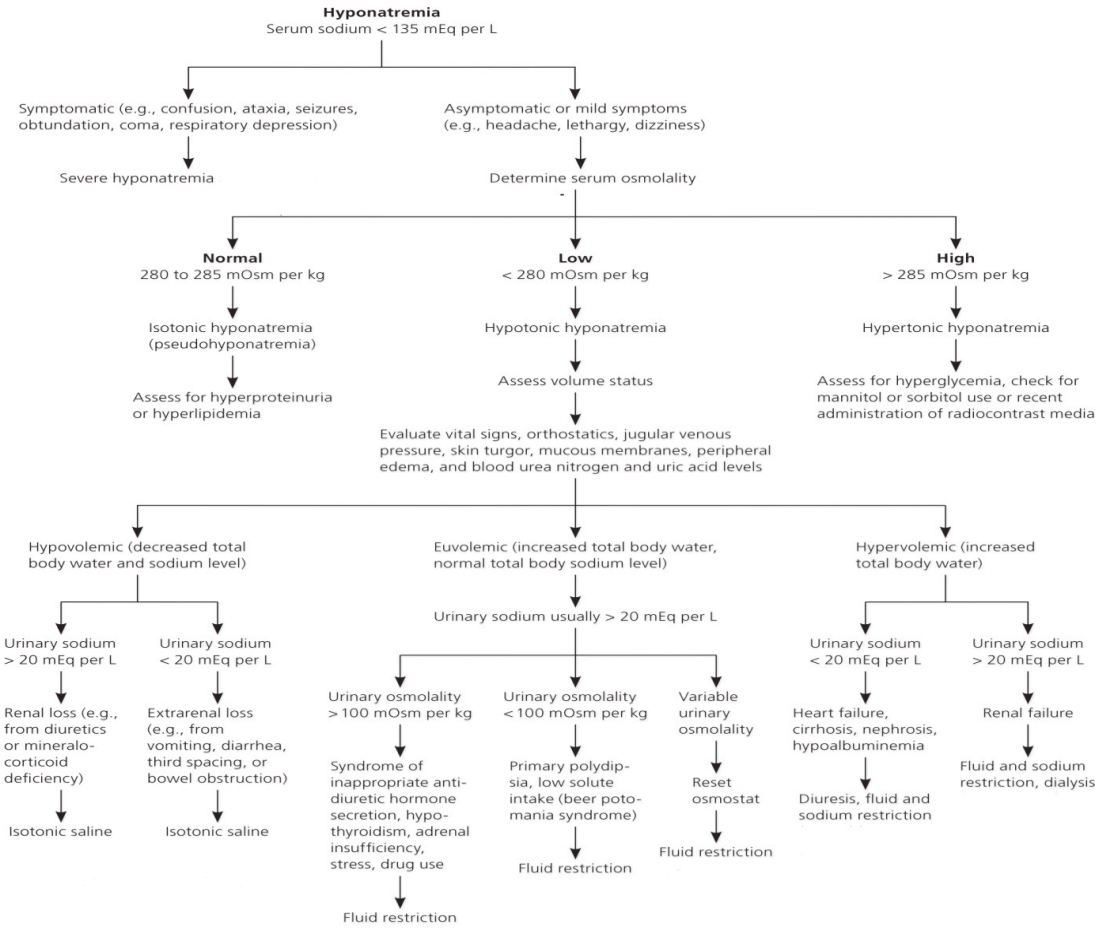
This Clinical criterion was made in 1967 by Schwartz and Bartter, which is still valid to date. No single best test is followed for diagnosis of SIAD. [5-7]

- Serum sodium less than 135mEq/L,
- Serum osmolality less than 275 mOsm/kg,
- Urine sodium higher than 40 mEq/L (due to ADH-mediated free water absorption from renal collecting tubules),
- Urine osmolality greater than 100 mOsm/kg and
- The absence of clinical evidence of volume depletion – normal skin turgor, blood pressure within the normal range, absence of various causes of hyponatremia (adrenal insufficiency, hypothyroidism, cardiac failure, pituitary insufficiency, renal disease with salt wastage, hepatic disease, drugs that impair renal



Source: Hayder M. Al-kuraishy, Ali I. Al-Gareeb, SafaaQusti, Eida M. Alshammari, Francis O. Atanu, Gaber El-Saber Batiha, Arginine vasopressin and pathophysiology of COVID-19: An innovative perspective, Biomedicine & Pharmacotherapy, Volume 143,2021,112193, ISSN 0753-3322.

Figure 1. Physiology of Arginine Vasopressin



Source: Am Fam physician.2015;92(6):430b-437.

Figure 2. Evaluation of Hyponatremia

water excretion, Correction of hyponatremia by fluid restriction). Renal function tests and random blood sugar tests are necessary to check hyperglycemia and uremia as these are the potential causes of pseudo-hyponatremia.

TESTS FOR SIADH

- Serum osmolality and serum sodium concentration
- urine osmolality and urine sodium concentration
- Renal function tests (BUN and Creatinine)
- Blood sugar random
- Thyroid profile
- Plasma AVP
- Serum cortisol
- Serum potassium
- Serum bicarbonate
- Serum chloride
- Fasting lipid profile
- Liver function tests

Before labeling a patient with SIAD, clinicians must rule out hypothyroidism and adrenal insufficiency. Further tests are required to find out underlying causes according to history. Patients with long-standing smoking history, weight loss, or pulmonary symptoms must have a chest X-ray and CT scan to look for small cell lung carcinoma.

DIFFERENTIAL DIAGNOSIS

- Acute Kidney Injury
- Addison's Disease
- Cerebral salt wasting
- Chronic Kidney Disease
- Exercise-induced hyponatremia
- Hypothyroidism with myxedema Coma
- Psychogenic Polydipsia.

TREATMENT

- From the time of identification, management of this syndrome was based on the underlying disease or the drug responsible.[FIGURE 2]
- If the removal of the primary cause was not possible, additional treatment options like fluid restriction, sodium administration via oral preparations, or in more severe cases continuous infusion of (3%) hypertonic saline or bolus can be considered.
- Other treatment approaches for SIAD, contemplated tetracycline (demeclocycline) and lithium. The former was considered since 1970 with limited results and poor accessibility, the latter was hampered by potentially significant adverse events and questionable efficacy. [8-10]
- Urea is a second-line potential treatment strategy, with a combination of low-dose diuretic and sodium chloride oral preparations.[11]However, this drug is hampered by low compliance, due to gastrointestinal side effects like nausea and efficacy-related issues, despite being at an accessible cost.
- In asymptomatic patients with mild hyponatremia, fluid restriction (500–800 ml/day) can be considered as the first option for a gradual normalization of sodium levels. However, this approach has low improvement due to poor compliance and requires more time to be effective in addition to renal function monitoring.
- Moreover, it should be managed meticulouslyin cancer patients with a higher risk of hypovolemic situations and the need for chemotherapeutic infusions. [12-14]
- In chronic hyponatremia, especially in asymptomatic patients, identification and removal of the primary cause of electrolytic imbalance can be more effective than elevating the serum sodium concentration.
- Infusion of hypertonic saline (3%) is highly recommended in acute situations with neurological symptoms.
- The guidelines advise a bolus of 100–150 mL in 10 minutes, which might be repeated 2 to 3 times until serum sodium increases by 5 mmol avoiding overcorrection. [15] Not more than 10 mmol in the first 24 hours, or 8 mmol if there are risk factors, must be reached to prevent severe damage to the central nervous system, such as central pontine myelinolysis and ultimately coma and death.
- The recommendation is to carry on the correction until symptoms disappear, with careful monitoring of the patient's conditions and serum sodium concentration to avoid hyponatremia overcorrection. If the patient is symptomatic but hyponatremia occurred chronically, correction should be performed more gradually (1.5 to 2 mmol/L/h).[16-18]
- The new therapeutic approach to SIAD-induced hyponatremia with the introduction of AVP-antagonistic agents specific for V2R named vaptans. Tolvaptan is leading among them, administered orally, and has been approved in the US and Europe for the treatment of euvolemic hyponatremia caused by SIAD.

TOLVAPTAN: Is a selective vasopressin V2-receptor antagonist administered orally, acts by promoting the excretion of free water (without loss of serum electrolytes) resulting in net fluid loss, increased urine output, decreased urine osmolality, and subsequent restoration of normal serum sodium levels. It is recommended for hyponatremia that is symptomatic, hypervolemic or euvolemic (serum sodium level less than 125mEq/L), or less severe hyponatremia that has not improved with fluid restriction alone. It corrects hyponatremia secondary to congestive heart failure, liver cirrhosis, and the SIAD. Having a narrow therapeutic index, it is advised to start or restart the medication only in a hospital setting to avoid an excessively quick correction of the hyponatremia. It is an expensive drug and makes you thirstier, which may restrict its effects.

CONCLUSION

Being the commonest cause of hyponatremia in hospitalized patients, SIAD has a significant impact on the outcome. Therefore, a correct diagnosis needs precise assessment of the patient's volume status and other underlying causes, although management has only been a fluid restriction for euvolemic hyponatremia, tolvaptan and similar drugs provide an opportunity to restore the physiological conditions in the patients.

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