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Pathophysiology, Diagnosis and Management of Hyponatremia: A Review

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Abstract: ***Hyponatremia is a multifactorial physiogical disorder characterized by serum sodium concentration less than 135 mmol/litre and contributing to 15-30% human blood osmoregulatory disorders. It may be euvolemic, hypovolemic or hypervolemic. The factors like severity, symptoms and nature of onset determines the type of treatment to be followed. Hypovolemic hyponatremia is normally treated by normal saline while 3% NaCl and fluid restriction are significant for euvolemic hyponatremia. Hypervolemic hyponatremia responds well to fluid restriction and diuretics. Judicious use of drugs like vaptans may help in treatment of hyponatremia. This review paper attempts to highlight a systematic approach towards diagnosis and management of hyponatremia.***

Keywords: Hyponatremia, Osmolality, Demyelination, SIADH, Vaptans

1. Introduction

Homeostasis in human body is maintained through a proper balance of various physiochemical and hormonal mechanisms. Any disturbance in these mechanisms may lead to a wide spectrum of clinical problems. A vital homeostatic mechanism among these involves regulation of electrolyte balance particularly serum sodium level. Normal serum sodium values are 135-145 mmol/Litre. A fall in the serum sodium concentration below 135 mmol/litre is clinically referred as hyponatremia. It is the most common blood osmoregulatory disorder caused due to the inability of the kidney to excrete a water load or excess water intake. The prevalence of hyponatremia is approximately 2.5% and 30% of patients are treated in the intensive care unit. 15–20 % of emergency admissions to hospital are due to hyponatraemia [1]. It is more common in elderly persons, patients on diuretics, infants, postoperative patients, and patients with malignancy [2]. Clinical symptoms of hyponatremia vary from subtle to severe or even life threatening [3, 4] and are associated with increased mortality, morbidity and length of hospital stay in patients presenting with a range of conditions. It must be understood that hyponatremia has no relation whatsoever with how the kidneys handle sodium, but how it handles free water [5]. The underlying mechanism for hyponatremia is concerned with abnormality in the ADH hormone secretion. ADH is secreted by the hypothalamus and released into the blood stream by the posterior lobe of pituitary gland. Its secretion is accelerated when the blood osmotic concentration increases that generates thirst signals. Thirst is sensed by osmoreceptors located in the hypothalamus and leads to the release of ADH hormone from the posterior pituitary. This hormone acts on the V2 receptors located at the basolateral aspect of the collecting duct cells of the kidney nephrons and promotes water absorption and abolishes thirst. Hyponatremia occurs if there is persistent ADH stimulation or abnormal ADH secretion as reported in Syndrome of inappropriate ADH release (SIADH).If the symptoms appear in less than 48 hours, hyponatremia is said to be acute and if they appear in time more than 48 hours, hyponatremia is said to be chronic. Acute hyponatermia is characterized by development of neurologic symptoms like seizures, impaired mental status, coma and death resulting from cerebral edema induced by water movement into the brain**.** Chronic hyponatremia is more common and asymptomatic**.** Patients suffering from chronic hyponatremia possess serum sodium concentration usually above 120 mmol/L. in this case; brain adapts itself by developing a protective mechanism that reduces the degree of cerebral edema by generation of idiogenic osmoles. Gastrointestinal tract symptoms like nausea, vomiting, loss of appetite and subtle neurologic abnormalities characterizes mild hyponatremia and serum sodium is between 120 and 130 mmol/L. Disturbances in the gait and frequent falls are reported in the elderly patients [6]. Normal serum osmolality is 280‑295 mmol/kg. The serum osmolality can be calculated by the concentration in millimoles per liter of the major serum solutes according to the following equation:

Serum osmolality (mmol/kg) = (2 × serum conc. of Na^+) +
(serum conc. of Glucose/18)
+ (conc. of blood urea nitrogen/2.8).

2. Types of Hyponatremia

Hyponatremia is of varied types like Iso-osmotic or pseudohyponatremia, Hyperosmotic or translocational hyponatremia and Hypo-osmotic or true hyponatremia.[Fig.1] Pathological conditions like multiple myeloma may causes increase in the concentration of plasma triglycerides or proteins that lead to Pseudohyponatremia, also referred as isotonic/iso-osmotic hyponatremia. In such situations, plasma water fraction becomes less than 80 percent [7,8] but the measured concentration of Na^+ gets reduced although there is no change in the total osmotic concentration of the plasma. If the plasma contains osmotically active solutes like glucose, the osmolality of plasma increases even there is reduced conc. of Na^+. This condition is referred as translocational or hypertonic hyponatremia [9].True hyponatremia is characterized by reduction in plasma osmolality synchronised with decrease in serum Na^+ concentration.

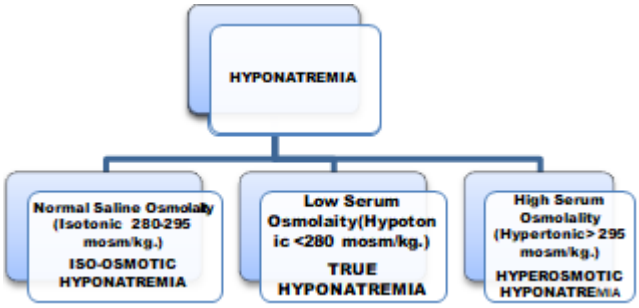

Figure 1: Types of Hyponatremia

3. Pathophysiology of True Hyponatremia

True hyponatremia may be caused due to hypovolemia, cerebral salt wasting, intake of diuretics and euvolemia. The euvolemic hyponatremia is most common and accountable for 60% cases of hyponatremia. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is found to be the commonest cause of euvolemia [10]. Pathogenesis of SIADH includes symptoms such as inappropriate ADH secretion, high urinary Sodium, increased ECF volume, normal/low urine volume and blood urea, decreased blood urea nitrogen/creatinine ratio and decreased plasma uric acid. It can be treated by fluid restriction and administration of furosemide drug. SIADH is generally diagnosed by the Schwartz criteria which are subjected to conditions like stopping the usage of diuretics within a week prior to diagnosis and the absence of other potential causes of hypo-osmolality. SIADH highlights the peculiar symptoms of euvolemic hyponatremia like measured serum osmolality less than 280 milliosmomoles/kg H_2O), urinary osmolality greater than100 milliosmomoles/kg H_2O,urinary Na^+ conc. greater than 40 mmol/L with normal dietary sodium intake, normal concentration of K^+ , normal thyroid, renal and adrenal function with no acid base disorders. The supporting diagnostic criteria for SIADH are serum uric acid<4 mg/dl, blood urea nitrogen <10 mg/dl, fractional sodium excretion >1%, fractional urea excretion >55%, failure to improve or worsening of hyponatremia after 0.9% saline infusion and improvement of hyponatremia with fluid restriction [11-13]. Pathophysiology of SIADH includes appearance of physiological symptoms such as CNS disturbances, Stroke, hemorrhage, infection, trauma, TB ,psychosis, malignancies, small cell carcinoma of lung, other lung tumors, head and neck cancer, olfactory neuroblastoma, extrapulmonary small cell carcinomas, pulmonary disease like pneumonia, asthma, acute respiratory failure, hormone deficiency hypothyroidism or hypopituitarism, HIV, hereditary SIADH, hereditary hypothalamic syndrome, nephrogenic syndrome of inappropriate antidiuresis, gain-of-function mutation in V2 receptor gene on X chromosome, loss of function mutation in transient receptor potential vanilloid type 4 (TRPV4) gene encoding a component of central osmolality-sensing mechanism in hypothalamus, idiopathic, exercise associated hyponatremia, low dietary solute intake, primary polydipsia [14,15]. There are certain drugs like antidiabetic drugs-chlorpropamide, anti epileptic drugs-carbamazepine, oxcarbazepine, selective serotonin reuptake inhibitors like fluoxetine, sertraline, anticancer drugs-Vincristine, vinblastine, vinorelbine, antipsychotic drugs-Thioridazine, monoamine oxidase inhibitors, pain killers, opiates, nonsteroidal anti-inflammatory agents, exogenous hormone administration- Vasopressin, desmopressin or oxytocin, ciprofloxacin which would increase the ADH secretion and its effect and likely to be one of the cause for SIADH. It has been reported that in case of normal person when plasma osmolality is below 280mosmol/kg, plasma ADH levels decreases leading to more excretion of diluted urine. This osmoregulatory mechanism raises the plasma tonicity to above 280 mosmol/kg by feedback mechanism leading to increase in the levels of ADH. SIADH which involves disturbances in the levels of ADH shows four different patterns: Type A, B, C and D. In SIADH type A, there is unregulated release of ADH irrespective of plasma osmolality. In this case, urine osmolality is very high due to increase in the levels of ADH. In SIADH type B, ADH level is modest and there is slow secretion or leakage of it. SIADH type C is characterized by normal and stable concentration of plasma Na^+. SIADH type D is rare and is characterized by normal osmoregulatory functioning but urine is concentrated even at low levels of ADH secretion. There are three underlying mechanisms for its occurrence-germ cell mutation causing activation of V2 Vasopressin receptor, antidiuretics and irregulatories in the transport of aquaporins water channels mediating ADH physiology. Hypovolemic hyponatremia may arises due to kidney disorder or some other non-renal factor like mineralocorticoid deficiency in which water is excreted in more quantity leading to decrease in the plasma volume. In cerebral salt wasting, kidney excretes water and salts in the urine. Pathogenesis of Cerebral salt wasting includes symptoms such as increased brain natriuretic peptide, hyponatremia , high urinary sodium, decreased ECF volume, high urine volume and blood urea, increased blood urea nitrogen/creatinine ratio, normal or decreased Plasma uric acid. Its treatment involves administration of normal saline and fludrocortisones rarely. Certain diuretics like thiazides induce hyponatremia in elderly females. It occurs due to increase in the water intake co-ordinated with fall in the diluting ability and water excretion in the distal convoluted tubule. It results in loss of sodium in the urine, hence, leads to decrease in the plasma conc. of sodium ion [16]. Some diuretics interfere with the countercurrent mechanism in the loop of Henle. It affects Na^+-K^+ exchange pump and prevents water retention mechanism by ADH hormone. The probability of loop diuretics in causing hyponatremia is found to be rare.

4. Etiological Factors for hyponatremia

There are a number of factors responsible for the development of symptoms and execution of hyponatremia like exercise, low dietary salt intake, primary polydipsia, and physiogical disorders of heart, liver and kidney. Exercise associated hyponatremia has been noticed in athletics due to excessive water intake with persistent ADH secretion [14,15].It has been reported that approximately 900 mosml of primary solutes like salts of Na^+ and K^+ along with urea is excreted out per day in case of normal person taking a normal diet. Low dietary salt intake has been reported in case of beer drinkers and in persons who take low protein and high water intake diets. They show drastic reduction in daily solute excretion from 900 mosml to less than 250 mosmol despite suppressed ADH [17].When there is an increase in the thirst signals referred as primary polydipsia,

ADH secretion get suppressed due to feed back regulation. It leads to excretion of excess amount of dilute urine along with excretion of salts, hence, may lead to fatal hyponatremia. Certain diseases like heart failure, acute and chronic kidney disease lead to hypervolemic hyponatremia.

5. Diagnosis of hyponatremia

In order to have proper diagnosis of hyponatremia, one should be aware about the drug and diet history of the patient along with clinical signs of hyponatremia such as vomiting and diarrhea, increase in the pulse rate, hypothyroidism or adrenal insufficiency, CNS or lung lesion [18].Blood biochemical analysis for hyponatremia includes analysis of serum/urine Na^+ levels, serum and urine osmolality, urine to serum electrolyte ratio, fractional excretion of sodium, serum uric acid and urea concentrations. Other investigations may be carried out to diagnose the hyponatremia such as thyroid profile, ACTH stimulation tests, CT/MRI of brain and imaging of chest. A number of biomedical instruments such as ion specific electrode (ISE) using direct potentiometry, ion-selective electrodes utilize indirect potentiometry and Flame photometers are employed to diagnose hyponatremia through measurement of serum Na^+ concentration [19,20]. In addition to these, analysis of serum osmolality with the help of osmometer may differentiate true, pseudo or translocational hyponatremia. Biochemical investigations of RBS, serum triglyceride and serum protein may further reflects serum concentrations of Na^+ in an indirect manner, for example, a decrease in the serum concentrations of Na^+ by 1.6 meq/l is detected with per mg increase in blood glucose above 100 mg/dl. Likewise there is fall in the serum concentrations of Na^+ by 1.0 meq/L for every 500 mg/dl rise in serum triglycerides above100 mg/dl. There is a fall of about 4.0 meq/L for every 1 gm/dl rise in serum protein above 8gm/dl. Urine osmolality investigations indicated that a hyponatremic patient show reduced values below 100 mosmol/kg and a specific gravity $\leq$1.003 due to excessive excretion of dilute urine and deficiency of ADH hormone. Hypovolemic and Euvolemic hyponatremia can be differentiated by urine sodium and urine chloride concentrations. It has been found that in case of hypovolemic hyponatremic patients who have metabolic alkalosis caused by vomiting, the urine sodium concentration may be greater than chloride. But if the concentration of both of these two ions in the urine is equal, it becomes difficult to differentiate between the two. In this case, administration of 1 litre 0.9% NaCl is done**.** In hypovolemic patient, infusion of 0.9% NaCl should inhibits the hypovolemic stimulus to ADH release, thereby increases the excretion of a dilute urine and hyponatremia get rapidly corrected. Since in SIADH patient, ADH release is independent of the volume status, hence, hypertonic urine is excreted even after 0.9% NaCl infusion and SIADH may not be corrected. In case of SIADH, blood urea nitrogen (Serum uric acid and urea concentrations) becomes lesser than 4 mg/dl due to excretion of these salts along with dilute urine. It has been found that in case of aged patients, urea excretion decreases, hence, blood urea estimation cannot be a correct diagnosis procedure in such cases [21,22].Urine to serum electrolyte ratio may be employed to diagnose the hyponatremia. It can be calculated by taking the sum of the urine sodium plus potassium concentrations divided by the serum sodium concentration. if this ratio is less than 0.5, it indicates high urine electrolyte free water and fluid restriction is adequate but if this ratio comes to be greater than one, it indicates urine is hypertonic, hence, water restriction is not sufficient and other therapeutic measures are necessary to correct the hyponatremia [23].Fractional excretion of sodium is also an indicator of the hyponatremia. It is less than 0.1% in case of patients with normal renal function, hypervolemic or normovolemic hyponatremia and greater than 0.1% indicates hypovolemic hyponatremia.

6. Treatment of hyponatremia

The treatment of hyponatremia can be done based upon certain factors like Volume status, duration of hyponatremia (whether acute/<48 h or chronic >48 h), presence or absence of symptoms and etiology of hyponatremia [19,20, 24, 25]. Acute euvolemic hyponatermia which has been reported in athletics, polydipsia patients and ecstasy users shows characteristic symptoms like brain herniation and rapid correction with 3% NaCl saline is required [26].Chronic hyponatremia is generally asymptomatic or has mild symptoms like seizures or confusion. In severe cases of chronic hyponatremia in which the patient may show serum concentration of sodium below 125 mmol/L, rapid correction therapy is needed as done in case of acute hyponatremia. In such cases, initial administration of 3% NaCl therapy is needed to raise the serum sodium by 4-6 mmol above baseline. Vasopressin antagonists may be employed. In case of chronic hyponatremia, the risk of cerebral herniation is very low. Hence, rapid correction therapy is risky as it can lead to demyelination of brain tissue and may results into a rare but severe disorder namely osmotic demyelination syndrome, formerly called central pontine myelinolysis [27-30]. It is due to the increase in the serum sodium levels. This syndrome is characterized by locked in syndrome i.e. quadriparesis with preserved vertical eye movements and cerebral edema. It has been recently found that demyelination syndrome can be reversed by relowering of sodium and administration of desmopressin [26,31]. osmotic demyelination is more prevalent in case of malnourished patients and alcoholics [32].In patients with low risk of demyelination syndrome, acute hyponatremia can be treated by 3% NaCl therapy but taking the control on serum sodium concentration maximally upto 10-12 mmol/L in 24 h. (maximum of 10 to 12 mmol/day according to recent guidelines) and in patients with high risk of demyelination syndrome, the serum sodium concentration be raised by a goal of 4 to 6 mmol/L per 24 h and by less than 9 mmol/L in any 24 h period (maximum of 4 to 6 mmol/day according to recent guidelines). The degree to which one liter of a given solution initially raises the serum sodium concentration in a hyponatremic patient, without any water or sodium losses in the urine, is estimated from the Adrogué-Madias formula, i.e

Increase in serum sodium =

$$\frac{\text{Conc. of sodium infuscate-serum concentration of sodium}}{\text{Estimated total body water+1}}$$

Rise in SNa = (Infusate [Na] – SNa) ÷ (TBW + 1)

Another formula was proposed to estimate both the sodium deficit and the direct effect of a given fluid (3% NaCl) on the serum sodium (SNa) concentration, for example:
Sodium deficit = Total body water (TBW) × (desired SNa – actual SNa).

However, these mathematical formulae have limitations and cannot be used to accurately predict the magnitude of change in serum sodium and frequent measurements are necessary. Calculation errors are possible even with the best formulas and frequent monitoring of the patient during therapy is absolutely essential to ensure optimal chances for recovery. Instead 1ml/kg of 3% NaCl is estimated to raise the serum Na^+ by 1mmol/l. In addition water restriction, salt, urea, demeclocycline and vaptans are used according to the etiology**.** 0.9% NaCl has a limited role in correction of the hyponatremia in SIADH and 3% NaCl is the fluid of choice. Careful monitoring of the serum sodium is essential to prevent very rapid correction. In case of fluid restriction, hard candy or ice chips for drinking fluids can be used to suppress thirst. Concurrent use of a loop diuretic is beneficial in patients with SIADH who have a high urine to serum electrolyte (>1). Furosemide inhibits the sodium chloride reabsorption in the thick ascending limb of the loop of henle and cause more of water loss than sodium loss (urine produced is like ½ normal saline). Thiazides should not be used. Other drugs used for chronic SIADH are urea, demeclocycline and the vaptans. Antipsychotic drug clozapine is useful in at least some psychotics.

7. Conclusion

Incidence of hyponatremia is increasing at a fast rate; hence, it becomes an important cause of morbidity and mortality. Since hyponatremia is of varied types, hence, proper guidelines should be followed to establish its correct etiology so that appropriate treatment could be started. However, caution should be exercised to ensure that the correction should be gradual to avoid hypernatremia or to rapid correction to avoid development of osmotic demyelination syndrome. More rapid correction should only be targeted in cases where there is certainty that the hyponatremia is acute or if the hyponatremia is causing severe neurological symptoms. Too rapid correction of hyponatremia may risk permanent severe neurological damage or death [32].

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