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(REVIEW ARTICLE)

A recent ongoing effect: Hyponatremia in neurologically ill patients

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Abstract

Different variables altering the volume of extracellular fluid might result in hyponatremia, which is defined as a serum sodium content below 136 millimoles per liter. Depending on the volume status, it can be classified as hypovolemic, euvolemic, or hypervolemic. Hyponatremia is caused by a number of risk factors and drugs, such as diuretics, NSAIDs, and antidepressants. Hyponatremia is more common in patients with neurological conditions, especially those with head trauma, subarachnoid hemorrhage, or acute meningitis. Recent advancements in analysis for disorder of antidiuretic hormone syndrome (SIADH), a prevalent cause, include vasopressin-2 receptor antagonists. The intricate regulation of sodium and water balance by humoral, neurological, and renal mechanisms is a part of normal physiology. Hyponatremia may result from medications such as tramadol, sacubitril/valsartan, antidepressants, and anticonvulsants interfering with these mechanisms. Drug-induced hyponatremia is managed by stopping the offending agent, limiting fluid intake, and occasionally administering hypertonic saline. For chronic hyponatremia, the use of vaptans, like tolvaptan, in conjunction with urea therapy is growing. A risky complication of hyponatremia is osmotic demyelination syndrome, which can occur when the condition is treated too quickly. To avoid negative consequences, close observation and the right amount of fluids must be administered during treatment. To summarize, treating hyponatremia effectively entails determining the underlying causes, treating them, and making sure that serum sodium levels are carefully corrected to avoid consequences such as osmotic demyelination syndrome.

Keywords: Hyponatremia; SIADH; Diuretics; hypovolemic; Euvolemic; hypervolemic; Over correction; Osmotic demylination syndrome; Drug induced hyponatremia

1. Introduction

"Hyponatremia" is the term used to describe a reduction in the serum sodium concentration to less than 136 mg/liter. Low, normal, or high tonicity are associated with hyponatremia, but hypernatremia is invariably a sign of hypertonicity. [1]. It is reasonable to categorise the etiology of hyponatremia according to the extracellular fluid's volume status. Extracellular fluid (ECF) primarily contains sodium, as was previously determined. The ECF volume can be used to classify hyponatremia as hypovolemic, euvolemic, or hypervolemic [2]. Renal illness, liver cirrhosis, and congestive heart failure can all result in hypervolemic hyponatremia. Although it might be challenging to distinguish between euvolemia and hypovolemia in a clinical setting, measuring plasma osmolality can be a helpful investigative tool [3]. They are classified into 130 to 134 mEq/L of sodium is considered mild hyponatremia. Between 120 and 129 mEq/L is considered moderate hyponatremia. Na level less than 120 mEq/L is considered as severe hyponatremia [4].

The risk factors of Hyponatremia are Surgery/injury, Fluid loss in conditions like (diarrhea, vomitting, excessive sweating, blood loss, pregnancy, menstruation), young/older age , Kidney malfunction , Adrenal insufficiency, Hypothyroidism, Cirrhosis & Heart failure. The drugs that induce Hyponatremia are Diuretics, NSAIDs, DDAVP, Antidepressants, SSRI, Antiepileptics [5].Several medications, including diuretics, anticonvulsants, and psychiatric medications, have been found to often cause hyponatremia in clinical practice. Drugs that interfere with the salt and

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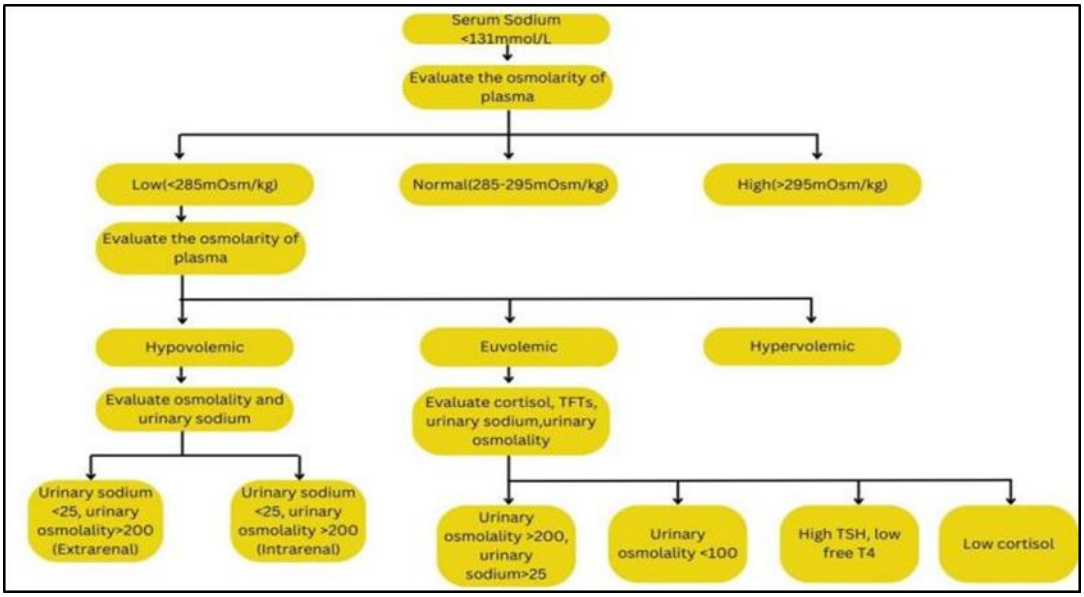
water balance or change the water homeostasis due to the syndrome of inappropriate antidiuretic hormone production can cause hyponatremia (such as diuretics) [6].

Among ion and water illnesses, hyponatremia is one of the most common. The most common cause is excessive renal water retention. Clinical signs and manifestations that are well-known are linked to severe hyponatremia (<125 mEq/L). Even slight reductions in blood salt levels, however, have been linked to higher death rates as well as a higher risk of fractures and falls. Even though just basic clinical and laboratory testing are needed, the diagnosis of hyponatremia can be challenging and intricate [7].

Most hyponatremia patients are asymptomatic and do not need to have their hyponatremia corrected right away. If you have symptomatic hyponatremia, you should get medical attention immediately to prevent the brain edema from getting worse. The onset of hyponatremia determines how quickly serum sodium levels should rise, a topic of ongoing discussion. Patients who have their serum sodium levels adjusted too quickly suffer the risk of developing central pontine myelinolysis; conversely, if the levels are adjusted too slowly, they suffer the risk of dying from brain herniation.Three main variables impact the treatment of hyponatremia: the degree of hyponatremia, which includes the existence or lack of serious brain-related symptoms like delirium, lethargy, seizures, and coma; the type of hyponatremia (acute or long-lasting, starting within 48 hours); and the volume status throughout treatment. Clinically significant hyponatremia is indicative of a medical emergency, especially if hypoxia is also present. It is advised to boost the SNa level by 4-6 hours by using hypertonic saline, which will cause a decline of 8–10 meq/L [8].

The main determinate of the osmolality of the plasma, which influences cell volume, is serum sodium. In a condition of low extracellular osmolality, cells will swell if there are not sufficient adaptive mechanisms to keep up cell volume. The most severe symptoms of hyponatremia occur in the brain when there is little to no response to an abrupt decrease in the blood's sodium content [9].

1.1. Classification [10]



2. Symptoms

2.1. Acute hyponatremia

Acute hyponatremia is characterized by the appearance of symptoms within 48 hours.Cerebral swelling is a result of fluid invading the brain in patients with severe hyponatremia, eliciting neurological signs which includes Coma, injury to the brain, convulsions, and even death are potential outcomes.

2.2. Chronic hyponatremia

Hyponatremia with a duration of more than 48 hours is referred to be "chronic." The majority of individuals have chronic hyponatremia. Serum typically contains more than 120 meq/L of salt. The brain adapts to hyponatremia by generating idiogenic osmoles. This prophylactic procedure reduces the severity of cerebral edema and starts on the first

day and ends in a few days. Consequently, those who have prolonged hyponatremia can not exhibit any symptoms. It is common for moderate hyponatremia to cause gastrointestinal symptoms such nausea, vomiting, and appetite loss **[11].**

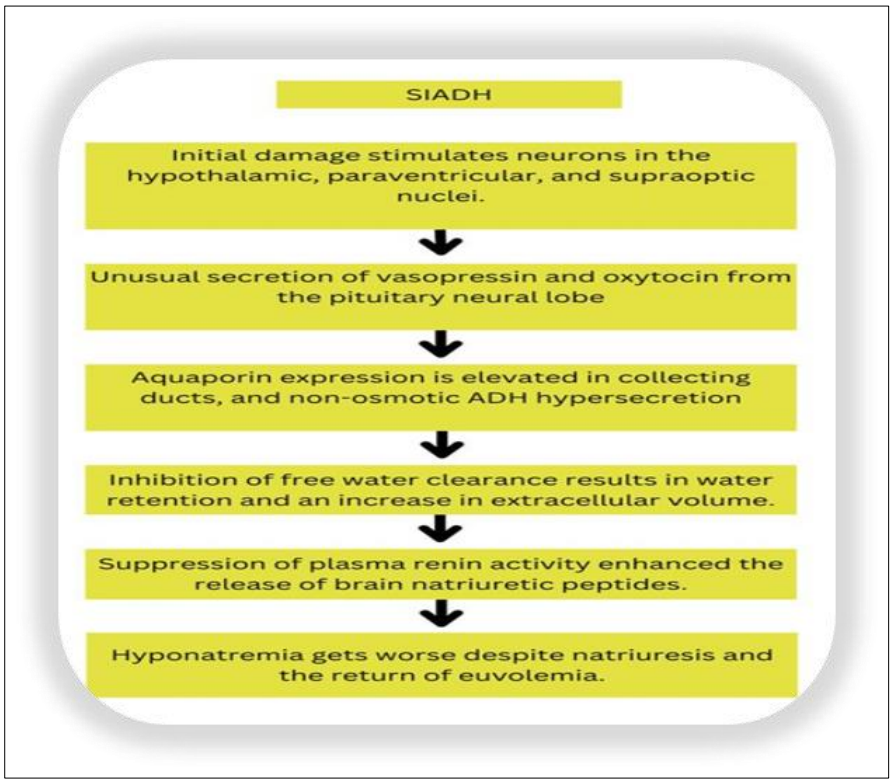
2.3. Epidemiology

A common definition of the reported incidence of hyponatremia is serum sodium levels below 135 mmol/L. This is the diagnostic threshold. There is a 7–60% increase in mortality associated with hyponatremia, which is observed in 1–15% of hospital inpatients. Moreover, mortality from acute hyponatremia is higher than that from chronic conditions. Compared to the general hospital population, neurologic patients have a higher prevalence of hyponatremia, which is specifically linked to aneurismal subarachnoid haemorrhage (SAH), traumatic brain injury (TBI), and basilar meningitis **[12].**

2.4. Risk factors

Patients with neurological diseases are more likely to experience hyponatremia, particularly if they are in critical condition. Patients with head injuries, subarachnoid hemorrhage (SAH), acute meningitis, and those following transsphenoidal surgery for pituitary tumor excision have all been reported to experience hyponatremia.The elderly population is especially susceptible to hyponatremia due to changes in renal function and fluid control that occur with aging **[13]**.

Pathophysiology [10]



2.5. Inappropriate antidiuretic hormone syndrome (siadh)

SIADH can be a biochemical manifestation of numerous illnesses, and it can also occasionally be the result of various fundamental aetiologies. The last ten years have brought about significant improvements in the management of SIADH, including the discovery of vasopressin-2 receptor antagonists, a powerful, condition-specific medication that targeted the fundamental pathophysiology of SIADH. This section addresses the principles behind the current SIADH treatment as well as evidence-based recommendations. Although fluid restriction is the first-line treatment for SIADH, we contend that it is either ineffective or not practical for an important proportion of patients, notwithstanding multiple recommendations and guidelines for treating hyponatraemia. The investigation offers multiple significant findings about the execution of water restriction **[14].**

2.6. Normal physiology of sodium and water regulation

Renal, humoral, and neural mechanisms regulate sodium and volume. These systems incorporate data on intravascular volume, circulatory hemodynamics, osmolality of extracellular fluid (ECF), and consumption of salt and water. Subsequently, humoral and neural messengers are employed to adjust sodium and water intake and excretion **[15].**

2.7. Water regulation

The major extracellular substances are sodium, glucose, urea, and its anions, bicarbonate and chloride. Intracellular osmolality is primarily controlled by potassium and its anions. Extracellular fluid (ECF) and internal fluid (IF) have the same osmolality as most cell membranes enable water to migrate across these easily. Water shifts carried on by significant variations in ECF osmolality can cause cells to contract or swell, which can have a major effect on cell function. The tonicity of the ECF is controlled by solutes that are difficult for cells to pass through, such as salt and glucose.ECF osmolality is mostly influenced by variations in water volume, while solute concentration fluctuations can also barely make a significant effect. Adrenaline vasopressin (AVP), also referred to as ADH, or antidiuretic hormone, or supraoptic and paraventricular nuclei of the hypothalamus, is produced and transported by neurons that are magnocellular to the posterior lobe of the pituitary gland. These neurons have responsibility for tracking variations in osmolality **[15]**.

2.8. Sodium regulation

Natriuretic factors and sympathetic innervation influence renal mechanisms that control sodium homeostasis. When sympathetic activity, hypotension, or the amount of salt supplied to the kidney's distal tubule is reduced, renal baroreceptors release more renin. The hormone angiotensin II binds the subcutaneous organ's receptors in response to renin, inducing thirst in addition to the non-osmotic production of AVP. The production of aldosterone is enhanced by angiotensin II. Aldosterone facilitates salt and water reabsorption in the nephron's distal tubule. The inner medullary collecting duct is the site of natriuretic peptide-induced natriuresis. These peptides includes urodilatin, brain or C-type natriuretic peptide [CNP], dendroaspis natriuretic peptide [DNP], atrial natriuretic peptide [ANP], and BNP [brain]. In addition to preventing sodium reabsorption, urolidilatin, BNP, and ANP can also cause an increase in sodium release. Furthermore, renin, aldosterone, and AVP secretion can be suppressed by circulating ANP and BNP **[15].**

2.9. Drug induced hyponatremia

Table 1 Drug induced hyponatremia

Tramadol-induced hyponatremia:	Tramadol is a synthetic opioid analgesic that acts centrally.In rare instances, this medication has been linked to hyponatremia. Antidiuretic hormone secretion may be increased as a result of its agonistic activity on morphinic receptors.Still, additional mechanisms contribute to its analgesic impact, such as increased serotonin release, which can trigger the secretion of antidiuretic hormones, as is also the case with selective serotonin reuptake inhibitors. Since this medication is frequently taken, it is important to be aware of this uncommon adverse effect. Caution is advised, particularly in older patients [16].
Sacubitril /valsartan induced hyponatremia:	Sacubitril/valsartan, which can be given to individuals with heart conditions and who have a lower fraction of ejection, is the first antihypertensive receptor neprilysin inhibitor (ARNI) authorised for use in the commercial market. The pair of medication contains both the neprilysin inhibitor sacubitril and the angiotensin II receptor blocker valsartan). We report on a case of an older patient who had low ejection fraction and heart failure, which we think had been brought on by ARNI-induced hyponatremia. The patient's use of sacubitril/valsartan and hyponatremia were obviously associated, based to the Naranjo's Adverse Drug Reaction Assessment score [17].
Anti-convulsants induced hyponatremia:	Although gabapentin, eslicarbazepine, sodium valproate, lamotrigine, and levetiracetam have all been connected to hyponatremia in epileptic patients, the anticonvulsants carbamazepine and oxcarbazepine are more commonly associated with hyponatremia. A wide range of patient groups (4.8% to 41.5%) may have hyponatremia produced by carbamazepine, depending on the research population. Older persons and those using medications known to cause hyponatremia, including thiazides, naturally have a higher chance of developing hyponatremia. The reasons for its growth could be bigger dosages of the medication, a lower starting serum sodium content, and elevated blood carbamazepine levels [18].

Antidepressants induced hyponatremia:	A number of psychotropic medications are linked to hyponatremia: benzodiazepines, antipsychotics (phenothiazines, butyrophenones), tricyclics, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, and monoamine oxidase inhibitors), and antidepressants.According to reports, hyponatremia has been associated with all antidepressants except mianserin. Whereas duloxetine, venlafaxine, and mirtazapine have the least correlations, citalopram's was the strongest.In individuals sixty years of age or older, the majority of antidepressant-related hyponatremia cases were linked to SSRIs, serotonin-norepinephrine reuptake inhibitors, and mirtazapine; tricyclic antidepressants, bupropion, and trazodone were less frequently linked to these effects, according to some recent research. Furthermore, hospitalization for hyponatremia is more likely to occur when SSRIs or venlafaxine are used than when tricyclic antidepressants and mirtazapine are used [19].

3. Management of drug induced hyponatremia

The most frequent anticonvulsants linked to hyponatremia in epileptic patients are carbamazepine and oxcarbazepine; additional anticonvulsants related with hyponatremia are gabapentin, eslicarbazepine, sodium valproate, lamotrigine, and levetiracetam. According to the research the population, a wide variety of patient groups (4.8% to 41.5%) may experience carbamazepine-induced hyponatremia. obviously older adults and those using medications known to cause hyponatremia, including thiazides, are more susceptible to hyponatremia. bigger blood levels of carbamazepine, greater quantities, or a lower beginning concentration of serum sodium could have been the cause of its rise. It is recommended to discontinue taking any medication that could end up in hyponatremia.

Drug-induced hyponatremia is treated in the same way as other fundamental SIAD therapy principles. The simplest, but least successful, way to restore water balance is water restriction. Furosemide at minuscule dosages can improve the solute-free water's clearance. It is recommended to boost oral consumption of salt and protein. If hyponatremia is mild and asymptomatic, perhaps all that is needed to bring serum sodium levels back to normal is to quit the offending agent and drink less water. Patients who have symptoms and are thought to have acute hyponatremia may benefit from 3% hypertonic saline injections to boost their serum sodium levels.Osmotic demyelination syndrome is currently rarely brought on by overcorrection; instead, it must be prevented by routinely checking serum sodium levels. For TIH patients, isotonic saline infusion in combination with or without a loop diuretic may be adequate to progressively correct hyponatremia.

Potassium replenishment will hasten the hyponatremia's recovery. It is important to take into account how potassium supplementation influences the concentration of salt in the serum. Because 1 mmol of retained potassium influences blood sodium levels as much as 1 mmol of retained sodium, even partial restoring of a potassium shortage without the use of sodium medication could result to an excessive rise in serum sodium. With that reason, hyponatremia overcorrection in situations involving potassium deficiency elevates the probability of osmotic demyelination.It is generally not recommended to re-administer the offending agent.

Thiazides shouldn't be administered to patients who have previously had TIH. It might be possible to keep using the potentially implicated medications in situations where patients have responded well to treatment, the hyponatremia is mild, and there is no other suitable course of treatment. However, since even mild hyponatremia may be linked to higher rates of morbidity and death, especially in the elderly, it is usually best to avoid it. Because chronic moderate hyponatremia affects mental abilities and changes movement, it raises the risk of falls. Therefore, there is a correlation between a slight hyponatremia and a greater chance of fractures in the bone.

Patients with osteoporosis and low bone quality may be more prone to fractures in hyponatremic circumstances.Even in people without a prior history of falls, fractures and low bone condition can increase the risk of fracture.An efficient and fairly affordable treatment option for mild chronic hyponatremia caused by SIAD is oral urea (0.5 g/kg). Urea has the ability to cause solute diuresis. As previously demonstrated, V2R is the primary mediator of most drug-induced hyponatremia. These drugs might compete with specific V2R antagonists for binding to the V2R. For these reasons, tolvaptan could be useful in treating hyponatremia caused by drugs in some people **[20]**.

3.1. Treatment for hypotonic hyponatremia

- ***Isotonic Saline:*** In patients with Na+ depletion; risk of autocorrection during therapy.
- ***Lift stringent Na^+ restriction:*** In patients with Na^+ excess.

- ***K^+ repletion :*** Must be given priority; prescription based on quantitative estimates; risk of overcorrection of hyponatremia.
- ***Vaptans:*** In euvolemic or heart failure patients with mild to moderate symptomatology; lift fluid restriction during initiation of drug: contraindicated in hyponatremic urgencies, hypovolemia, & underlying liver disease **[21].**

4. Treatment for chronic hyponatremia:

4.1. Vaptans

Vaptans function as antagonists on vasopressin receptors. The V1a, V1b, and V2 types of vasopressin (ADH) receptors are the three types that exist. The production of adrenocorticotropic hormone (ACTH) and vasoconstriction are the results of the V1a and V1b receptors, respectively, whilst antidiuresis is brought on by the V2 receptor. An increase in water loss (aquaresis) is the result of vasopressin receptor antagonists; nevertheless, the excretion of potassium and sodium remains unchanged. The best physiological strategy for treating hyponatremia is to use ventans, as they don't cause electrolyte depletion and don't require fluid restriction. They don't compromise renal function or activate the neurohormonal system.

Both intravenous and oral versions are available.

- Intravenous Relcovaptan (V1A-specific; V1RA)
- Conivaptan is nonselective (mixed V1A/V2).
- Nelivaptan is selective for V1B (V3RA).

Some examples of V2 selective (V2RA) compounds include Lixivaptan, Moxavaptan, Satavaptan, and Tolvaptan,Conivaptan and tolvaptan are now the only drugs accessible in India [22].

Supplementing CHF medication with disappearing salts is the favoured method of treating hyponatremia by lowering the dosage of diuretics. Trials, however, reveal varying serum sodium levels and ambiguous post-treatment instructions. Risks associated with medication interactions with saptans include improper usage for specific kinds of hyponatremia and ineffectiveness in treating vasopressin-independent SIADH. Examples of these medications are conivaptan and tolvaptan. High prices and scant data about their usage in kids should be taken into account [23].

4.2. Urea

Renal fluid excretion is increased by urea due to the induction of an osmotic diuresis. In the 1980s, Decaux and associates were among the first to employ urea not only for SIAD but also for other types of hyponatremia. More recently, Soupart et al. examined the use of urea and satavaptan for the treatment of 12 individuals with SIAD (both treatment periods were 1 year). Fascinatingly, the effectiveness and side-effect profiles of both treatments were comparable. While urea does not stop overcorrection, it can lessen the chance of the resulting brain injury. Histologic examination revealed that urea enhanced astrocyte viability and decreased demyelination, microglial activation, and alterations in the blood-brain barrier, in contrast to the two other therapies.While urea does not stop overcorrection, it can lessen the chance of the resulting brain injury. Histologic analysis revealed that urea enhanced astrocyte viability and decreased demyelination, microglial activation, and alterations in the blood-brain barrier, in contrast to the two other therapies [24].

4.3. Saline and hypertonic saline

Different forms of hyponatremia can be treated with different tonicities of fluids. The fluid selection is selected by the degree, root cause, and associated symptoms of hyponatremia. Hypovolemic hyponatremia is usually managed by isotonic saline solution. In some situations of severe dehydration (serum sodium <120 mEq/l), hypotonic fluid may eventually need to be provided. Since non-osmotic vasopressin release is inhibited when euvolemia is restored, overcorrection is more likely to occur. This can be confirmed by urine osmolality monitoring.Hypotonic fluids may also be necessary for some disorders, especially primary dizziness, which is associated with low serum vasopressin levels and diluted urine.When SIADH is the cause of symptomatic isovolemic hyponatremia, hypertonic saline (3%) is recommended as an alternative to isotonic saline. In some situations where lowering urine osmolality is necessary, loop diuretics may be added [25].

4.4. Syndrome of osmotic demyelination

Osmotic demyelination syndrome may arise in patients having a serum sodium concentration below 115 mEq/L and chronic hyponatremia, even when the levels of blood sodium adjustment are less than 10 mEq/L throughout a 24-hour period. When blood sodium is less than 115 mEq/L and the patient has severe hyponatremia and risk features, we suggest limiting serum sodium correction to fewer than 8 mEq/L. In patients with hyponatremia whose diet hasn't been enough, supplementing with thiamine is suggested. Preventing ODS could serve as a therapeutic limitation during the duration of medication for ongoing hyponatremia.Patients at the average risk of ODS should be medicated to a serum sodium (SNa) correction limit of 10–12 mEq/L in any 24-hour period and 18 mEq/L in any 48-hour period, as advised by the American Expert Panel [26].

4.5. Causes of overly rapid correction

A hyponatremia that is rectified rapidly enough can be caused by two things: (1) therapy that aims to increase the sodium concentration (like beginning a vasopressin antagonist or hypertonic saline); or (2) preventing exogenous desmopressin treatment or reversibly stimulating the production of antidiuretic hormone (ADH). Overcorrection of hyponatremia is frequently observed, particularly in individuals with severe hyponatremia (serum sodium <120 mEq/L).If renal function is normal, excess water is quickly removed (a process known as autocorrection) when the ADH release cause eliminates it and the urine's osmolality drops below 100 mosmol/kg.

4.6. Serum sodium autocorrection may occur in the following conditions such as

The serum sodium may autocorrect under the following conditions when saline is given to patients who truly suffer volume loss. The extra water is quickly evacuated, allowing people who have insufficient adrenal glands access to glucocorticoids, since the half-life of ADH production is rapidly restricted on recovery of euvolemia.

Cease to use drugs that cause dysregulated ADH secretion syndrome (SIADH). Selective serotonin reuptake inhibitors, desmopressin, and carbamazepine are a few of them. Desmopressin is used to treat arginine vasopressin deficiency, hemophilia, von Willebrand disease, nocturnal enuresis in children, and nocturia in adults. Those who drink a lot of water, however, may get hyponatremia as a result.

Reducing the amount of drugs used that cause inappropriate ADH secretion syndrome (SIADH). Selective serotonin reuptake inhibitors, desmopressin, and carbamazepine are a few of them. Desmopressin is used to treat arginine vasopressin deficiency, hemophilia, von Willebrand disease, nocturnal enuresis in children, nocturia in adults, and it can induce hyponatremia in those who drink a lot of water.

Due to their obstruction of urine dilution, thiazide diuretics should be discontinued.The use of an antagonistic vasopressin receptor during therapy.The abrupt remission of a short-term cause (e.g., surgical stress, illness, or pneumonia) for SIADH.Use of an antagonistic vasopressin receptor during treatment [27]

Abbreviations

NSAIDs- Nonsteriodal anti- inflammatory drug SIADH -Syndrome of inappropriate antidiuretic hormone ADH release, ECF- Extracelluar fluid, DDAVP- 1 desamino- 8-d-arginine vasopressin, SSRI- Selective serotonin reuptake inhibitor, TFT- Thyroid function test, SAH- Subarachnoid hemorrhage, TBI- Traumatic brain injury, ADH- Antidiuretic hormone, CNP- C-type natriuretic peptide, DNP- Dendroaspis natriuretic peptide, ANP- Atrial natriuretic peptide, BNP- Brain natriuretic peptide, ARNI- Angiotensin receptor/ Neprilysin inhibitor, TIH- Tumor induced hypocalcemia, ACTH- Adrenocorticotropic hormone, CHF- Congestive heart failure, ODS- Osmotic demylination syndrome

5. Conclusion

Hyponatremia, a frequent electrolyte imbalance, can be brought on by a variety of illnesses, including heart failure, drugs, neurological problems, and renal dysfunction. Its symptoms, which vary from mild gastrointestinal discomfort to severe neurological manifestations like seizures and coma, are categorized according to serum sodium levels. How hyponatremia is treated depends on its kind, severity, and underlying cause. Treatment options include fluid restriction, vasopressin receptor antagonists (vaptans), hypertonic saline injection, and urea therapy. Osmotic demyelination syndrome can result from too quick a correction of serum sodium levels, so caution must be exercised. In cases of hyponatremia, especially in patients with neurological illnesses, it is essential to comprehend the underlying mechanisms and appropriate management strategies in order to optimize patient outcomes.

Compliance with ethical standards

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Authors' contributions

- ***Dr. Milagrin Xavier :*** Critically reviewing and the manuscript for intellectual content, clarity, and accuracy.
- ***K. Aishwarya, Raveena Rajesh Kumar, J. Subiksha :*** Composing: Draft Preparation: Creating the draft of the manuscript.
- **Writing**: Analyzing and modifying what is written to make sure that it is precise, apparent and has intellectual content.

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