Review

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Hyponatremia in the Neurologically Ill Patient: A Review

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Abstract

Hyponatremia is a well-known disorder commonly faced by clinicians managing neurologically ill patients. Neurological disorders are often associated with hyponatremia during their acute presentation and can be associated with specific neurologic etiologies and symptoms. Patients may present with hyponatremia with traumatic brain injury, develop hyponatremia subacutely following aneurysmal subarachnoid hemorrhage, or may manifest with seizures due to hyponatremia itself. Clinicians caring for the neurologically ill patient should be well versed in identifying these early signs, symptoms, and etiologies of hyponatremia. Early diagnosis and treatment can potentially avoid neurologic and systemic complications in these patients and improve outcomes. This review focuses on the causes and findings of hyponatremia in the neurologically ill patient and discusses the pathophysiology, diagnoses, and treatment strategies for commonly encountered etiologies.

Keywords

hyponatremia, SIADH, cerebral salt wasting, sodium, encephalopathy

Introduction

Hyponatremia is frequently encountered in the hospital ward and intensive care unit and is a common component of neurologic diseases, present in up to 38% to 54% of patients.[1,2] Hyponatremia and water balance have profound effects on the injured brain. Hyponatremia is associated with up to a 60% increase in mortality when present following acute brain injury.[3] The clinical symptoms associated with hyponatremia relate to the severity and rate of change of serum sodium concentrations. Hyponatremia is defined as serum sodium concentration of <135 mEq/L. Acute hyponatremia develops over a period of <48 hours, whereas chronic hyponatremia may be present for more than 48 hours or over an unclear duration. The severity of hyponatremia is defined by serum sodium concentration:

- Mild hyponatremia: Na concentration 130 to 134 mEq/L
- Moderate hyponatremia: Na concentration 120 to 129 mEq/L
- Severe hyponatremia: Na concentration <120 mEq/L

Clinical symptoms may range from mild headache and confusion to seizures, coma, or even death (Table 1).[4] Given the significant role hyponatremia may play in the clinical course of the neurologically ill patient, early recognition and appropriate treatment are critical to preventing potential complications.

Pathophysiology of Hyponatremia and Effects on the Brain

The body maintains normal sodium levels due to the kidneys' function of excreting free water.[5] The link between brain volume and sodium concentration is tightly regulated in part by specific osmoreceptors in the hypothalamus expressing transient receptor potential cation channels that allow for sodium regulation.[6] Normal osmoregulation (mediated by the subfornical organ in the brain) associated with hyponatremia results in decreased thirst and antidiuretic hormone (ADH) secretion.[7] Excessive ADH (also known as arginine vasopressin) secretion remains the most common cause of hyponatremia in hospitalized patients.[8] Antidiuretic hormone is responsible for

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Table 1. Clinical Neurologic Manifestations Associated With Hyponatremia.

Acute Hyponatremia	Chronic Hyponatremia
Nausea and vomiting	Nausea and vomiting
Headache	Fatigue
Seizure	Gait instability and falls
Respiratory arrest	Attention deficits
Coma and/or death	

water homeostasis by binding to V2 receptors in principal cells of the renal collecting duct resulting in aquaporin insertion and water collection into the highly concentrated medullary interstitium.[9] Figure 1 summarizes this hypothalamus–ADH–renal loop.

The pathophysiology of hyponatremia's effect on the brain is complex due to both acute and chronic means of cerebral adaptation. Hyponatremia typically results in decreased serum osmolality and generation of an osmotic gradient which results in movement of water into glial and neuronal cells. Initially, interstitial fluid migrates into the cerebrospinal fluid which is displaced to the thecal sac and systemic circulation.[10] In the acute setting, hypotonicity is rapidly managed preventing substantial cellular swelling. Neurons can excrete osmotically active molecules, namely glutamate, and ions (sodium, potassium, and chloride) which decrease the osmotic gradient and result in loss of water from neurons.[7,10,11] Surrounding astrocytes are able to protect neurons from active swelling by transfer of osmotically active amino acids including taurine.[7] This allows neurons to maintain normal volume while the astrocytes subsequently swell. This dynamic process initiates within minutes and is capable of sustaining for hours.[11] Astrocyte volume is restored over a more extended time period as they extrude additional osmotically active osmolytes including polyalcohols and methylamines.[10] The entire process can continue for up to 48 hours, while concurrent downregulation of water-handling channels (aquaporin) may take up to a week or longer before reaching homeostasis.[12]

Rapid correction of chronic hyponatremia can thus lead to additional neurologic injury in the setting of these adaptive changes. Correction of hyponatremia results in new osmotic gradients between the intracellular and extracellular compartments. The resultant movement of water out of the intracellular compartment results in a rapid increase in the intracellular concentration of electrolytes as well as a decrease in the intracellular volume, effectively resulting in cerebral dehydration.[10] A delicate balance must be struck when attempting to correct hyponatremia, resulting in clinically severe symptoms to minimize risks of permanent neurologic symptoms and possibly death. Those at highest risk of developing osmotic demyelination and cerebral edema are patients with sodium concentrations <106 mEq/L (well below the traditional high-risk definition Na <120), hypokalemia, alcoholism, malnutrition, and advanced liver disease.[13,14]

Differential Diagnosis for Hyponatremia in the Neurologically Ill Patient

Cerebral salt wasting

Pathophysiology. Although there is a clear association between cerebral salt wasting (CSW) and severe neurologic disease, the underlying pathophysiology remains unclear. One

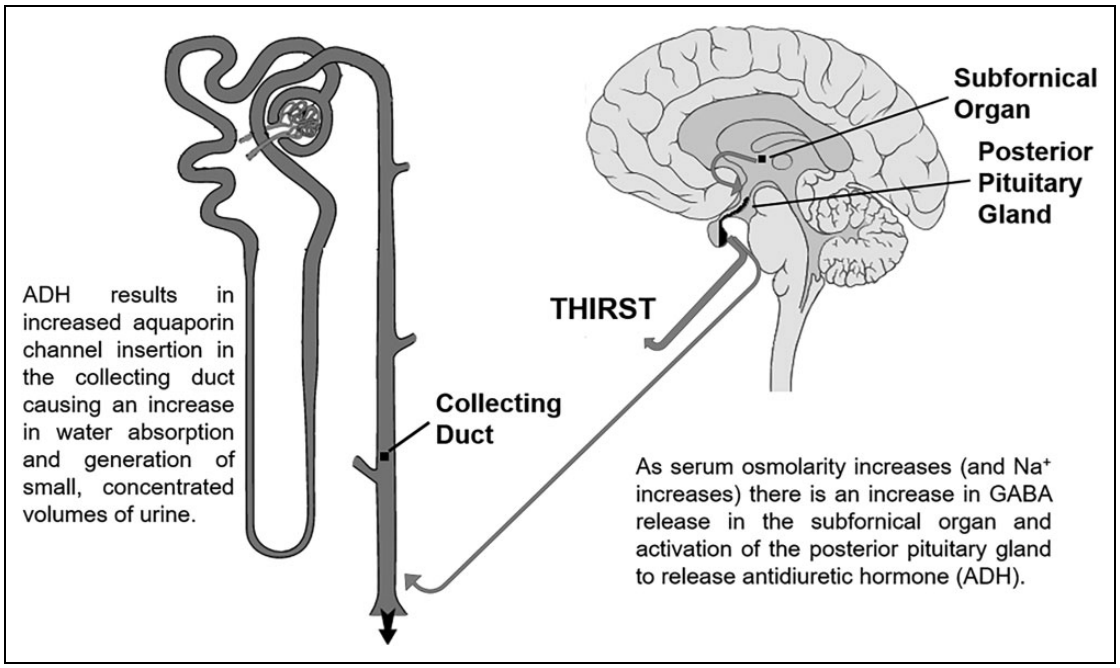

Figure 1. Hypothalamus–antidiuretic hormone (vasopressin)–renal loop.

prevailing theory is based on the dysregulation of the sympathetic nervous system. With a loss of adrenergic tone to the nephron, there is a resultant decrease in renin secretion and ultimate decrease in sodium reabsorption along with dilation of the afferent arterioles leading to increased glomerular filtration.[15] This theory does have limitations as there is typically an increase in sympathetic tone shortly after neurologic injury, as demonstrated by neurogenic pulmonary edema and neurogenic heart failure.[1] However, CSW does not typically present in the hyperacute setting but rather presents several days after initial presentation. A separate pathophysiology that may be related to CSW includes the excessive excretion of natriuretic peptides.[16] There are 4 main natriuretic peptides with C-type natriuretic peptide mainly produced in the telencephalon, hypothalamus, and endothelium.[17] The natriuretic peptides also cause dilation of arterioles and venules by blocking vascular sympathetic tone, thereby increasing glomerular filtration as well as inhibiting sodium reabsorption at the proximal convoluted tubule and collecting duct.[18] Adrenomedullin, a potent vasodilator with natriuretic properties, has been proposed as a potential mediator of CSW.[19] Although the serum concentration of this peptide peaks rapidly after experimental subarachnoid hemorrhage in mice, the cerebrospinal fluid levels do seem to parallel the development of hyponatremia.[19,20]

Diagnosis. Cerebral salt wasting is classified as a hypovolemic hyponatremic state. The clinical features are[1]:

- Hypovolemia
- Hyponatremia (Na <135 mEq/L) and hypo-osmolality (<280 mOsm/kg)
- Elevated urine osmolality (>300 mOsm/kg)
- Elevated urinary sodium (>40 mEq/L)

The laboratory findings are similar as in syndrome of inappropriate antidiuretic hormone (SIADH) secretion. Because of this, the accurate assessment of the patient's volume status is paramount. The clinical assessment of volume status and responsiveness to intravenous (IV) fluids has limited sensitivity, and no single test will predict fluid responsiveness. The assessment of volume status is still riddled with debate and is outside the scope of this review. Static assessments of volume status that may be used include capillary refill, skin turgor, oral secretions, urine concentration, and mucous membrane hydration. Dynamic measurements that may also prove helpful include a passive leg raise test, inferior vena cava ultrasound, Swan-Ganz catheter placement, stroke volume variation, and/or pulse pressure variation from arterial waveform analysis.

Treatment. The treatment of CSW is of utmost importance as incorrect diagnosis and treatment can lead to increased risk of delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage, increased mortality, and worsening hyponatremia.[21] Standard treatment for CSW is replacement of the sodium and water deficit. The first step in management is to correct hypovolemia with isotonic fluid, namely normal saline. Although euvolemia can be achieved, this may not correct the hyponatremia. Additional treatment options include the use of hypertonic saline, usually in concentrations of 1.5% to 3%, administration of salt tablets, and/or use of mineralocorticoids. Mineralocorticoids, namely fludrocortisone, are commonly used to treat CSW, and although these can achieve eunatremia, they have not been demonstrated to improve outcomes or decrease rates of cerebral vasospasm.[22] There is little evidence on what treatment to use for hyponatremia and at what threshold of hyponatremia warrants treatment. In those with neurologic injury, even eunatremia (serum Na concentration 135-145 mEq/L) may not be considered optimal. Human et al published a retrospective review on sodium management in acute neurologic injuries including subarachnoid hemorrhage, traumatic brain injury, brain tumor, and intraparenchymal hemorrhage. The sodium level that resulted in treatment was different in each disease state (range: 132-135 Na mEq/L), and the initial treatment differed slightly, although not statistically significant.[2] Commonly, hypertonic saline is started but the optimal concentration and dosing regimen remain unknown. There is general clinical equipoise between the uses of bolus versus infusion of hypertonic saline.

Syndrome of Inappropriate Antidiuretic Hormone Secretion

Pathophysiology. Syndrome of inappropriate antidiuretic hormone is a disorder of inability to suppress the secretion of ADH resulting in impaired water excretion.[23] In normal individuals, the hypothalamic osmoreceptor cells respond to the plasma osmolality by grading the secretion of ADH, but those with SIADH have impaired the regulation of ADH release.[24] There are 5 patterns of dysfunction:

- Supraphysiologic ADH levels that are unresponsive to osmotic changes. This is suggestive of ectopic secretion of ADH.[25]
- Abnormally low osmotic threshold for ADH release. This is commonly called the "reset osmostat."[24]
- Persistent production of physiological levels of ADH that is not responsive to changes in plasma osmolality.[25]
- Although there is normal regulation of ADH release, urine remains concentrated. Potential mechanisms for this disconnect include vasopressin-2 receptor gain of function or production of an antidiuretic compound other than ADH.[24]
- The decline in plasma ADH during hypertonic saline infusion possibly due to altered baroreceptor signaling.[25]

Table 2. Medications Associated With Syndrome of Inappropriate Antidiuretic Hormone.

Antiepileptic Medications	**Psychiatric Medications**
Carbamazepine	Butyrophenones (haloperidol)
Lamotrigine	Monoamine oxidase inhibitors
Oxcarbazepine	Phenothiazine (fluphenazine, chlorpromazine)
Sodium valproate	Risperidone
Oncologic Medications	Selective Serotonin Reuptake Inhibitors
Alkylating agents (cyclophosphamide)	Tricyclic antidepressants
Ifosfamide	Venlafaxine
Imatinib	**Miscellaneous**
Methotrexate	Amiodarone
Platinum (cisplatin)	Bromocriptine
Vinca alkaloids (vincristine)	Ciprofloxacin
Pain Medications	Desmopressin or Vasopressin
Non-steroidal anti-inflammatory	Ecstasy (methylenedioxy methamphetamine)
Opiates	Interferon-alpha

Table 3. Differentiating Cerebral Salt Wasting and Syndrome of Inappropriate Antidiuretic Hormone.

	Cerebral Salt Wasting	Syndrome of Inappropriate Antidiuretic Hormone
Extracellular volume status	Decreased	Unchanged
Heart rate	Unchanged to increased	Unchanged
Body weight	Decreased	Unchanged
Urine output	Unchanged to increased	Unchanged to decreased
Hematocrit	Increased (relative to baseline)	Unchanged
Blood urea nitrogen	Increased	Unchanged
Serum bicarbonate	Increased	Unchanged
Serum urate	Unchanged to decreased	Unchanged
Urine osmolality	>100 mOsm/kg	>100 mOsm/kg
Urine Na excretion	>40 mmol/L	>40 mmol/L

There are multiple causes of abnormal ADH release and these can be grouped into several categories: central nervous system (CNS) disturbance, malignancy, medication, pulmonary disease, postsurgical, abnormal hormone homeostasis, and infectious. Central nervous system disturbances including ischemic or hemorrhagic stroke, trauma, and infection can enhance ADH release due to direct hypothalamic and pituitary dysfunction.[23] Malignancies, most commonly small-cell lung cancer, result in ectopic ADH secretion.[26] There are numerous medications that can result in increased ADH release or enhance the effect of ADH on the renal collecting duct (Table2).[27] Surgical- and procedural-related hyponatremia is often due to hypersecretion of ADH in response to pain.[28] The use of vasopressin, in shock, desmopressin, in von Willebrand disease, or oxytocin, in labor induction, can all result in hyponatremia due to increased vasopressin receptor activity.[29]

Diagnosis. Syndrome of inappropriate antidiuretic hormone is defined by the following features[23]:

- Decreased effective osmolality (<275 mOsm/kg)
- Urinary osmolality >100 mOsm/kg
- Clinical euvolemia
- Urinary sodium >40 mmol/L
- No recent diuretic use, normal thyroid, and adrenal function.

The significant overlap between SIADH and CSW can make initial diagnoses challenging; however, key differences are highlighted in Table 3.

Treatment. Given the extensive differential diagnoses for the etiology of SIADH, the determination of the underlying cause and treatment will result in sustained normalization of sodium levels. Stopping unnecessary medications, treatment of underlying infection, or pain control will result in sodium correction, but this may be delayed. Fluid restriction remains the most common therapy for SIADH, as the increase in total body water is corrected due to a daily net negative water balance. The goal intake is less than 800 mL/d and will typically result in an increase of 2 mEq/L during the first 24 hours of therapy.[30] The use of oral medications such as demeclocycline and lithium, which act to decrease the responsiveness of the vasopressin receptor to ADH and thereby increasing water excretion, is limited by nephrotoxicity and delay in treatment to response by several days to 1 week.[31]

In those with severe hyponatremia requiring more rapid correction, administration of IV sodium chloride may be required. It is important to understand, for sustained sodium increase, the sodium concentration of the IV fluid must exceed the concentration in the urine. A simplified explanation of this principle is as follows: sodium and water excretion are regulated by independent systems, aldosterone, and ADH, respectively. Administration of IV saline will result in unchanged excretion of sodium at the same concentration prior to administration of IV fluid. If the concentration of IV fluid is less than the urine concentration, there will be excess free water within the IV fluid which will drive sodium concentrations lower. There is a transient increase in serum sodium with administration as the concentration of sodium in the IV fluid is greater than that of the serum. If, on the other hand, a more concentrated IV saline solution is administered, the amount of free water that needs to be excreted to maintain the same urine

electrolyte concentration increases and thereby decreases the total body water content.

Another oral and delayed treatment for SIADH is increasing the oral solute load. As in the prior explanation, if the urine electrolyte excretion is fixed, then increasing the total intake of solute via salt tablets, urea, or high-protein diet can increase the amount of water excretion. Use of these treatments will induce increases in urine output.

The last class of medications available for the treatment of SIADH are vasopressin receptor antagonists, "vaptans," which act mainly on the V2 receptors in the collecting ducts to increase water excretion.[32] There are 2 current Food and Drug Administration–approved vaptans for use in euvolemic and hypervolemic hyponatremia—IV conivaptan and oral tolvaptan. Conivaptan is administered as a loading bolus of 20 mg over 30 minutes followed by 20 to 40 mg continuous infusion over 24 hours and can be continued up to 96 hours. It is unique as a vasopressin receptor antagonist as it also has activity at the V1a receptor which may provide additional benefit in hyponatremia due to congestive heart failure.[33] Conivaptan has been evaluated for those with neurologic injury including severe traumatic brain injury, which showed early response (higher serum sodium and lower intracranial pressure at 4 hours).[34] Specifically, in patients with neurologic injury and severe hyponatremia or clinically significant hyponatremia, conivaptan leads to higher serum sodium at 6, 24, and 36 hours, but this study was too small to demonstrate safety or clinical benefit.[35] Tolvaptan has also been studied in a number of chronic hyponatremic conditions including cirrhosis, heart failure, and SIADH. In the Study of Ascending Level of Tolavaptan in Hyponatremia (SALT) 1 and 2 trials 1, there was an increase in serum sodium 134 to 135 mEq/L versus 130 mEq/L at day 4 and 136 mEq/L versus 131 mEq/L at day 30. However, there are limited data on long-term mortality and morbidity associated with underlying cause of hyponatremia, but there appears to be no benefit with tolvaptan.[36] Given the unpredictable response between individual patients, clinical utility of vaptans in comparison to hypertonic saline infusions alone remains limited.[37]

Osmotic Demyelination Syndrome

Pathophysiology. Osmotic demyelination syndrome (ODS) is a rare but feared complication of sodium correction. Osmotic demyelination syndrome has replaced the term central pontine myelinolysis as extrapontine involvement both with and without pontine involvement has been demonstrated.[38] The exact pathophysiology of ODS is not completely understood; however, because this process is delayed over several hours to days, rapid correction of acute hyponatremia is not likely to result in ODS.[39] The risk factors for ODS include severe hyponatremia (<120 mEq/L) present for more than 2 to 3 days, alcoholism, malnutrition, and concomitant hypokalemia.[40] Special consideration needs to be given to patients with cirrhosis as even moderate hyponatremia (>120 mEq/L) and correction can result in ODS, especially following liver transplantation.[41]

Diagnosis. Osmotic demyelination syndrome is typically delayed for 2 to 6 days after rapid correction of serum sodium.[40] Clinical signs can vary from mild to striking psychomotor changes including psychiatric changes, catatonia, limb tremor, myoclonus, parkinsonism, and paresis/plegia of any and all limbs including bulbar musculature.[42] Despite early neurologic symptoms, imaging may remain normal for as long as 4 weeks after onset and normal imaging does not exclude the diagnosis of ODS.[43] The finding of classic magnetic resonance imaging is diffusion restriction within the central pons with characteristic trident pattern that predates T2 signal changes.[44]

Treatment. Because the clinical symptoms of ODS will lag behind the sodium correction, it has been advocated that rescue therapy may play a role and has been demonstrated in animal models.[45] Rescue therapy, those that have exceeded the recommended sodium increases, with desmopressin (DDAVP) and/or 5% dextrose solution in water (D5W) can re-lower serum sodium. Consideration for bolus dose of D5W at 6 ml/kg ideal body weight over 2 hours (will drop Na by 2 mEq/l), or DDAVP 2 µg IV or subcutaneously every 6 hours (can be escalated to 4 µg).[46] Experimental treatments include minocycline and dexamethasone, which demonstrate some efficacy in animal models,[47] but no randomized human data exist.

Although ODS can be neurologically devastating, there is growing evidence that there can be substantial improvement. Small case series have demonstrated recovery in those that survive to modified Rankin scale of ≤ 1 in approximately one-third of patients, debilitated but independent in one-third of patients, and full dependence in one-third of patients.[48] Despite severe functional disability at presentation, this is not related to final outcome. These patients will require prolonged hospital stay as well as rehabilitation, but there remains possibility for meaningful neurologic recovery.[49]

Clinical Relevance

Subarachnoid hemorrhage, traumatic brain injury, ischemic and hemorrhagic stroke, CNS infections, and brain tumors can be complicated by hyponatremia in 33% to 54% of cases.[4,15,50] Varying degrees and duration of hyponatremia determine the therapeutic needs. However, in those cases where a neurologist is assisting with care, moderate to severe symptoms warrant immediate treatment.[51]

The severity of symptoms associated with hyponatremia remains the most clinically relevant indication for prompt treatment. Mild symptoms include headache, fatigue, nausea, dizziness, forgetfulness, and gait disturbances and are commonly associated with chronic hyponatremia. Although the serum sodium concentration may be "severe" (Na

Table 4. Recommendations on Treatment of Hyponatremia.

		US Recommendations	European Recommendations
Severe symptoms	Self-induced acute water intoxication, known duration <24-48, intracranial pathology or increased intracranial pressure, seizures, or coma Vomiting, cardiorespiratory distress, abnormal or deep somnolence, seizure, and coma	100 mL 3% NaCl bolus over 10 minutes up to 3 doses to manage symptoms	150 mL 3% NaCl bolus over 20 minutes. Recheck Na and repeat 150 mL 3% NaCl bolus Goal Na rise 10 mmol/L/d, then 8 mmol/L/d, and thereafter to 130 mmol/L/d • If no increase can repeat • If no improvement 3% NaCl with goal 1 mEq/L/h to <10 total increase
Mild to moderate symptoms	At-risk Na <120 mEq/L of >48 hours duration. Nausea without emesis, confusion, and headache	3% NaCl infusion at 0.5-2 mL/kg/h	250 mL 3% NaCl bolus over 20 minutes. Goal 5 mEq/L increase over 24 hours
Chronic hyponatremia		Minimum correction of Na 4-8 mEq/L, and if high risk, then 4-6 mEq/L	Avoid increase >10 mEq/L in the first 24 hours, then >8 mEq/L daily
Acute hyponatremia without symptoms			Stop fluids or the factors contributing to hyponatremia If Na decrease >10 mEq/L, treatment with 150 mL 3% NaCl over 20 minutes.

concentration <120 mEq/L), brain adaptation to minimize cerebral edema makes life-threatening complications such as increased intracranial pressure less common.[52] Severe symptoms include seizure, obtundation, and coma and are typically associated with acute hyponatremia.[51]

For acute neurologic presentations of hyponatremia, increasing serum sodium concentration by 4 to 6 mEq/L can reverse impending herniation or stop seizure activity.[53] The European guidelines recommend rapid infusion of 3% saline depending on severity of symptoms—those noted above would be considered "severe"—with two 150-mL boluses over 20 minutes with a sodium level assessment between boluses. US expert panels recommend 100 mL 3% bolus over 10 minutes repeated 3 times as needed for symptom management in "severe" clinical cases. The rate of correction for acute, symptomatic hyponatremia should be 8 to 10 mEq/L in the first 24 hours, but the SALT studies used a safety threshold of 12 mEq/L in 24 hours, so there is underrepresentation of over-rapid correction using these drugs.[54] Table 4 summarizes the current clinical treatment recommendations for hyponatremia.[13,55]

Hyponatremic encephalopathy. Hyponatremic encephalopathy is the term broadly used to define neurological dysfunction during hyponatremia. It is thought to be due to a combination of parenchymal edema and elevated intracranial pressure resulting in relative oligemia and hypoxia.[56] A sodium drop of greater than 1 mEq/L/h is associated with neurological sequelae and death.[57] The spectrum of mild cognitive changes to stupor and eventually coma is related to a number of physiologic factors. The early findings of hyponatremic encephalopathy include impairment in gait and attention. Other subtle more difficult to recognize early symptoms include headache, nausea, lethargy, confusion, and even agitation.[58] Acute and chronic mechanisms allow for brain water regulation, with chronic compensatory mechanisms providing significant protective adaptations, making the laboratory parameters of hyponatremic encephalopathy difficult to define.[53]

Additional risk factors to develop hyponatremic encephalopathy exist outside of absolute serum sodium concentration and rate of change in serum sodium concentration. Permanent sequelae are associated with younger age and premenopausal women.[56] Children under the age of 16 years are at increased risk due to the relatively larger brain to intracranial volume ratio.[59] Brain volume begins to decrease in the third decade of life, making older patients at lower risk for elevation in cerebral edema and symptomatic hyponatremia.[60] The risk of death or permanent neurologic sequelae from hyponatremic encephalopathy is substantially greater in premenopausal women as compared to both men and postmenopausal women.[61]

Hyponatremic encephalopathy is also associated with noncardiogenic pulmonary edema. Mainly reported in postoperative patients, the hypothesized physiology is similar to that of other diseases that result in rapid increases in intracranial pressure.[62] Rapid elevation in intracranial pressure results in a catecholamine surge, which in turn results in pulmonary vasoconstriction and capillary wall injury.[63] Early identification and treatment with hypertonic saline can reverse the process. Approximately 1% of postoperative patients have hyponatremia and 20% of these patients are acutely symptomatic.[5]

Hyponatremia and cerebral edema. The development of cerebral edema is a widespread pathological condition that may affect patients with a variety of neurological diseases including ischemic stroke, hemorrhagic stroke, infection, neoplasm, and traumatic brain injury. The pathophysiology of cerebral edema development secondary to hyponatremia is unique, in comparison, due to a failure of brain adaptation to osmotically driven forces.[64] The chronicity of this failure to adapt influences the treatment strategy for sodium correction. In acute and severe cases, regardless of the mechanism of cerebral edema development, the subsequent failures in maintaining cerebral perfusion pressure and brain compression lead to neurologic injury and even death in severe cases. Given the lack of clinical trials targeting cerebral edema due to hyponatremia itself, current standard treatment protocols are extrapolated from other settings of cerebral edema management.[53] Previous studies have suggested that targeting hypernatremia (sodium concentrations of 145-155 mEq/L) may correlate with reduction in intracranial pressure and cerebral edema.[65] Hypertonic saline boluses have been used to treat elevated intracranial pressure and cerebral edema.[66] Increases in plasma sodium by 5 to 6 mEq/L is sufficient to decrease the intracranial pressure by 5 to 10 mmHg.[67] There is an ongoing debate regarding the rate and method of sodium correction in the setting of cerebral edema, and further clinical trials are warranted to address this.

Hyponatremia and seizures. Moderate to severe hyponatremia is also associated with seizures and even status epilepticus. Typically, seizures associated with hyponatremia are generalized, but focal seizures may be present.[68] The electroencephalogram (EEG), consistent with other metabolic encephalopathies, demonstrates ranges of diffuse slowing and altered reactivity generally correlating with the rate of change in electrolytes rather than the absolute level.[69] The etiology of acute seizure was due to moderate hyponatremia in 5% of cases.[70] Multiple case series report the use of hypertonic saline bolus with rapid correction of serum sodium resulting in control of seizures and corrections as small as 5 mmol/L can be sufficient to improve symptoms and result in seizure control.[71] Extrapolating from pediatric studies, sodium concentration should be corrected at a rate of 0.5 mEq/L/h, but higher rates (1-2 mEq/L/h) of correction have been used in young patients and appear to be well tolerated.[72] Correction of the metabolic disturbance is paramount and administration of an antiepileptic drug may not be necessary if the underlying disturbance is corrected.[73]

Conclusion

Hyponatremia is a common entity in hospitalized patients and particularly in patients with neurological illnesses. Neurologists are often consulted when the degree of hyponatremia is severe enough to present with a neurological manifestation such as seizures, cerebral edema, or even coma. Cerebral salt wasting and SIADH are key disorders that neurologists should be able to differentiate between and guide appropriate treatment. Early diagnosis, monitoring, and the appropriate treatment of hyponatremia and the underlying disorder/provoking factor, if identified, are vital in ensuring the best outcomes in this patient population.

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