Review

Sodium Disorders and Traumatic Brain Injury: A Narrative Review

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Review

Sodium Disorders and Traumatic Brain Injury: A Narrative Review

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Abstract: Traumatic brain injuries (TBI) cause direct central nervous system injury. The presentation depends on the location, the type, and the injury severity. Additional injury may develop secondary to compression, disruption of cerebral perfusion, and changes in sodium levels resulting in either cellular edema or dehydration. Plasma osmolality (Posm) is a critical parameter influenced by solute concentrations, including sodium, glucose, and urea, and is a relevant concern when considering sodium levels in these patients. While Posm can be calculated using a standard formula, direct measurement via osmometry offers better accuracy. It is essential to differentiate between osmolality and tonicity; the latter refers specifically to effective solutes that drive water movement in the extracellular fluid. Sodium and its anions are effective solutes, whereas urea and glucose have variable effects due to their permeability and insulin dependence. Following TBI, dysregulation of osmoregulation may occur and affect neurological outcomes. Osmoreceptors in the brain regulate arginine vasopressin secretion in response to changes in effective solute concentrations, with sodium chloride and mannitol being potent stimuli. The regulation of plasma osmolality, typically maintained within ±5% of a 280-295 mOsm/kg H_2O range, is crucial for homeostasis and relies on antidiuresis and thirst mechanisms. This review underscores the complexities of osmoregulation in the context of TBI and its clinical implications, particularly concerning the development of conditions, such as diabetes insipidus, syndrome of inappropriate antidiuretic hormone, and abnormal thirst.

Keywords: traumatic brain injury; blood brain barrier; diabetes insipidus; syndrome of inappropriate antidiuretic hormone secretion; thirst; hyponatremia; hypernatremia

1. Introduction

Patients with traumatic brain injury (TBI) have complex presentations. Important factors in these presentations include the type of injury, the location of the injury, and the severity of the injury. The classification of these patients often uses three items: the Glasgow coma scale, the time needed to recover consciousness, and the time of post-injury amnesia. Factors that influence outcomes include the individual's age, underlying comorbidity, and access to specialized treatment facilities. The consequences of injury can be analyzed as acute events during hospitalization and chronic complications posthospitalization. Additional injury after the initial trauma event likely develops when patients have increased intracranial pressure, increased intracranial bleeding, decreased brain blood flow secondary to hypotension or vasospasm, seizures, and abnormal electrolytes resulting in cellular dysfunction, i.e., dehydration or edema.

All classification systems used in patients with TBI have relatively poor performance characteristics in the prediction of long-term outcomes. This is especially true in patients with mild TBI who can have unpredictable courses, and in these patients, additional markers of brain injury might help predict outcomes. Brain biomarkers have been studied and do have potential utility [1,2]. However, these markers do not add to or improve current models for predicting outcomes at 6 and 24 months following TBI, and they do not seem useful in patients with mild TBI. However, in these latter patients, biomarkers have the potential to help characterize the clinical course, and if there is a second peak in the biomarkers, such as S100B, that would suggest ongoing neuronal injury.

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Elias et al. published a scoping review that analyzed the early management of older individuals following TBI [3]. Important concerns include the prior use of anticoagulants, which increase the risk of intracranial bleeding, the need to consider the possibility of intracranial lesions using computed tomography to evaluate patients at presentation, and the increased need for hospitalization for observation. This review did not discuss medical complications related to concussions. Potential concerns include seizures, increased neurologic disability with a risk for falls, and confusion with poor decision-making. Comorbidity, especially dementia and hypertension, increases the frequency of poor outcomes. Other investigators have published reviews of randomized control trials that described the early management of patients with either concussion or TBI [4]. In general, these trials do not discuss the hospital management of electrolytes and other medical abnormalities in these patients. The American College of Surgeons Trauma Program has published best practice guidelines for the management of TBI in 2024 [5]. The treatment goals recommended in this guideline include a serum sodium in the range of 135 to 145 mEq/L and a serum osmolality ≤320 mOsm/kg. Smith et al. reported the outcomes of 151 patients who presented to a trauma center [6]. Patients were classified into two cohorts, hyponatremia with an admission serum sodium of less than 135 mEq/L and non-hyponatremia. Hyponatremia had a significant association with mortality (45.5% died) and was an important predictor of mortality in a multiple regression analysis.

This review will consider the importance of extracellular fluid osmolality and regulation in cellular homeostasis in TBI and the disruption of the blood-brain barrier in TBI in the pathogenesis of complications. It also analyzes the important electrolyte abnormalities that can develop after TBI; these include diabetes insipidus, the syndrome of inappropriate antidiuretic hormone syndrome secretion, and primary thirst disorders in these patients. These disorders can cause very abnormal sodium levels and have important effects on brain cellular function that need immediate attention during the management of these patients.

2. Epidemiology of Traumatic Brain Injury

The Centers for Disease Control and Prevention publishes information on the annual number and rate of deaths per 100,000 TBIs in the United States [7]. There were 60,565 TBI-related deaths in 2018 and 60,611 deaths in 2019. The 2019 rate ranged from 1.3 per 100,000 in children aged 5 to 9 to 76.7 per 100,1000 in adults 75+ years of age. The adjusted rate was approximately three times higher in men. The rate of unintentional motor vehicle crash deaths was 3.1 per 100,000 for all ages, the rate for unintentional falls was 5.5 per 100,000 for all ages, and the rate for suicide was 7.5 per 100,000 for all ages. The adjusted rates for all ages in these three categories were higher in men than in women. Flores-Sandoval et al. (2024) published a systematic review of studies reporting mortality and disposition in adults with moderate to severe TBI [8]. This review included 64 studies published between 1992 and 2022. Mortality was higher in adults older than 60 years of age than in younger adults. In addition, older adults (> 65 years of age) were less likely to be discharged home than younger adults and were more likely to be discharged to skilled nursing facilities, inpatient rehabilitation, and palliative or hospice care.

The complexity of TBI makes it difficult to identify factors that provide good predictions of outcomes at 6, 12, and 24 months. The International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) and Corticoid Randomization after Significant Head Injury (CRASH) prognostic models have been used to predict 6-month unfavorable outcomes and mortality [9,10]. The IMPACT model includes core components (age, motor score, and pupils), core components + CT (hypoxemia, hypotension, CT results [level of diffuse injury], subarachnoid hemorrhage, and epidural mass), and core components + CT + lab (glucose and hemoglobin). The CRASH model includes country, age, Glasgow coma score, pupil reactions, and major extracranial injury. The areas under the curves in these two models for 12- and 24-month outcomes were approximately 0.8 with a sensitivity of 0.82 to 0.85 and a specificity of 0.52 to 0.54 [11]. Iderdar et al. published a systematic review and meta-analysis of studies reporting outcomes at 3 and 12 months following TBI [12,13]. Poor outcomes were associated with increased age, low Glasgow coma scores, poor pupil reactivity, increased intracranial pressure greater than 20 mm Hg, low hemoglobin levels, and higher glucose levels. No single factor

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consistently predicted mortality. Other factors associated with unfavorable outcomes included a midline shift of more than 5 mm, hypotension, hypoxemia, the requirement for blood transfusion, the requirement for mechanical ventilation, and intraventricular hemorrhage.

These studies have reported the profound consequences of TBI and the complex care these patients often need. The following sections discuss the electrolyte disorders associated with TBI and their clinical consequences.

3. Volume and Osmolality Control in Traumatic Brain Injury

Plasma osmolality (Posm) is primarily determined by the concentrations of solutes in plasma, including anions, glucose, and urea. It can be calculated using the standard formula commonly used by clinicians:

Posm (mmol/kg) = 2 X serum Na^+ (mEq/L) + glucose (mg/dl) / 18 + BUN (mg/dl) / 2.8.

However, the most accurate assessment of osmolality is obtained by direct measurement with osmometry using either freezing point depression or vapor pressure techniques. When discussing body osmolality, it is important to differentiate between osmolality and tonicity. Tonicity refers to the concentration of effective solutes in plasma, specifically those confined to the extracellular fluid (ECF) and unable to cross cell membranes into the intracellular fluid (ICF). Effective solutes, such as sodium and its accompanying anions, promote water movement between the ECF and ICF along osmotic gradients. In contrast, urea is not considered an effective solute, since it freely permeates cell membranes; the effect of glucose depends on insulin concentrations which are required for cellular uptake. Therefore, the effective plasma osmolality or tonicity can be calculated using the previously mentioned formula, excluding BUN:

Posm (mmol/kg) = 2 X serum Na^+ (mEq/L) + glucose (mg/dl) / 18.

The law of osmosis explains water movement across semipermeable membranes—those allowing water but not solutes to pass. When a semi-permeable membrane separates two compartments, water molecules will diffuse into the area of higher solute concentration. Thus, an increase in free water in the ECF will prompt water movement across the membrane, resulting in intracellular expansion, while a decrease in free water in the ECF will cause water to shift from the ICF to the extracellular space.

Osmoreceptors in the brain detect solute concentrations and modulate the secretion of arginine vasopressin (AVP) from the posterior pituitary. Only effective solutes stimulate AVP secretion; studies have demonstrated that solutes like sodium chloride and mannitol are significantly more effective than urea or glucose in this process [14]. Plasma osmolality is rigorously regulated within a ± 5% tolerance, with a normal range of 280-295 mOsm/kg, driven by tonicity rather than total osmolality. Two primary mechanisms maintain effective Posm: the pituitary secretion of AVP, which promotes antidiuresis, and the thirst response which compensates for water losses. Each mechanism is governed by distinct regulatory processes.

The neurohypophysis constitutes the location where AVP is synthesized in the paraventricular and supraoptic nuclei, subsequently transported down the pituitary stalk, and then released into capillaries from neuron terminals in the posterior pituitary. Damage to this region, such as from TBI, may not lead to diabetes insipidus, if the AVP-producing cell bodies in the hypothalamus remain intact, since AVP can be released from higher hypothalamic areas.

The vasopressin gene encodes a 154-amino-acid prohormone that undergoes cleavage into three peptides: neurophysin, AVP at the amino terminus (comprising 9 amino acids), and copeptin at the carboxy terminus. Copeptin is released in equimolar amounts with AVP; due to its larger size and longer half-life, it serves as the preferred surrogate marker for AVP secretion. Once in circulation, AVP interacts with three primary receptor subtypes: V1a, V1b, and V2. The kidneys are exquisitely sensitive to changes in plasma AVP, and urine volume is inversely proportional to AVP concentration. Specifically, lower AVP levels result in increased urine excretion, and in cases of complete central diabetes insipidus, urine excretion rates may reach up to 1,000 milliliters per hour. Physiological urine concentration occurs with plasma AVP levels in the range of 0.5 to 5.0 pg/ml. Although baroreceptors are less sensitive to AVP levels, they also stimulate its release in response to

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changes in blood pressure and blood volume exceeding 10-15% [15]. Thirst correlates linearly with fluctuations in plasma osmolality, but this response is not simultaneous with AVP secretion. A higher threshold for plasma osmolality, typically 5-10 mOsm/kg, is required to stimulate thirst compared to AVP release, thus positioning AVP as the primary osmotic regulator [16,17].

The thirst center is anatomically distinct from AVP-producing neurons and has been identified by positron emission tomography studies in the anterior midcingulate cortex; however, both centers receive input from osmoreceptors [18]. The primary osmoreceptors are located in the anterior wall of the third ventricle, extending from the anterior commissure to the organum vasculosum of the lamina terminalis (OVLT), collectively referred to as the AV3V area. The OVLT, positioned outside the blood-brain barrier, allows for rapid sensing of changes in plasma osmolality, which stimulates both thirst and AVP secretion [19].

Traumatic lesions affecting AVP neurons result in decreased AVP secretion, leading to diabetes insipidus characterized by polydipsia and polyuria. Conversely, a lesion in the anterior hypothalamus that damages osmoreceptors can lead to both a loss of AVP secretion and an absence of thirst and produces a disorder called adipsic diabetes insipidus. These patients are often chronically hyperosmolar, indicating that AVP secretion alone is insufficient to maintain water homeostasis. Diagnosing this condition can be challenging, as patients are unable to secrete AVP in response to hyperosmolar stimuli but can respond to hypovolemic stimuli. This combination reflects selective dysfunction of osmoreceptors, consistent with the understanding of various baroreceptor pathways within the brain [20,21].

Blood Brain Barrier Disruption

Traumatic brain injury causes significant disruption of the blood-brain barrier (BBB), which can contribute to secondary injury mechanisms. This disruption typically occurs within hours of the initial injury and can persist for years in some patients. The breakdown of the BBB allows serum proteins, such as fibrinogen and immunoglobulin G, to extravasate into the brain parenchyma, a phenomenon observed in both acute and chronic cases of TBI [22].

The disruption of the BBB contributes to the development of cerebral edema through two primary mechanisms. The first is vasogenic edema, characterized by the accumulation of fluid in the perivascular space. This fluid accumulation can lead to alterations in cerebral blood flow and increased intracranial pressure. The second mechanism is cytotoxic edema, which involves the activation of ion channels that facilitate water influx into intracellular spaces, further compromising the integrity of the BBB. If not promptly addressed, these processes can result in irreversible tissue damage and cell death, significantly contributing to the high mortality rates associated with severe TBI [22]. In most cases, the extent and location of disruption of the BBB are unknown, but these disruptions likely contribute to progressive brain injury.

In summary, injury to the hypothalamus and pituitary can cause changes in the secretion of AVP and in thirst responses. Both increases and decreases in these two homeostatic processes can lead to abnormal sodium concentrations and intracellular and extracellular fluid volumes, resulting in additional cellular injury. Disruption of the BBB also contributes to fluid accumulation at sites of injury.

4. Diabetes Insipidus

4.1. Etiology

Diabetes insipidus (DI) is a hormonal disorder that results in large volumes of dilute urine. There are several clinical disorders associated with polyuria; these include central and nephrogenic DI, primary polydipsia, and rarely gestational DI. Most central diabetes insipidus (CDI) cases occur after destruction of vasopressinergic neurons by TBI, neoplasms, neurosurgical procedures, or autoimmune inflammation involving the AVP-secreting neurons [23]. Nephrogenic diabetes insipidus (NDI) is the result of resistance of the kidneys to AVP due to mutations in the gene encoding AVP receptor 2 (*AVPR2*) or aquaporin 2 (*AQP2*), an adverse drug effect, or an electrolyte disorder

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[24]. Drug effects are most commonly caused by lithium or tricyclic antidepressants. Primary polydipsia is characterized by excessive fluid intake that leads to polyuria, despite intact AVP secretion and an appropriate antidiuretic renal response [24]. Gestational DI develops secondary to degradation of ADH, which is caused by the enzyme vasopressinase. All disorders with DI result in a water diuresis due to the inability to concentrate the urine.

4.2. Epidemiology

Diabetes insipidus is a rare disorder and has prevalence of 1 in 25,000. It can present at any age, and there is no gender predisposition. Central diabetes insipidus can be acquired or hereditary and occurs in 20% of moderate or severe cases of TBI and in 15% of nontraumatic subarachnoid bleeds [23]. The predominant manifestations of DI include hypotonic polyuria with urine output of greater than 50 mL/kg in 24 hours and polydipsia with fluid intake greater than 3L/day. In pregnancy, CDI may develop secondary to lymphocytic hypophysitis [23]. In addition, a pre-existing partial CDI in pregnant women may become more apparent due to the metabolic effects of placental cysteine aminopeptidase, an enzyme that increases metabolic clearance of oxytocin and AVP [23]. Therefore, in patients with TBI and DI, the possibility of DI secondary to causes other than TBI should be considered.

Traumatic brain injury commonly occurs following motor vehicle accidents, assaults, or falls. This injury can cause swelling around the hypothalamic-pituitary axis or direct damage to the paraventricular neurons, supraoptic hypothalamic neurons, the pituitary stalk, and axon terminals in the posterior pituitary. These abnormalities can be transient if the supraoptic and paraventricular neurons form new vascular connections or can become permanent [25]. Transient DI is often seen with transsphenoidal surgery for pituitary tumors or sella/suprasellar lesions. When transient, the post-traumatic DI can last a few days to a few weeks and is associated with a high mortality rate, particularly when it occurs very early after a TBI [26].

4.3. Diagnosis

The diagnosis of DI is confirmed with a 24-hour urine collection measuring urine volume and osmolality levels and measurement of plasma osmolality, sodium levels, and copeptin levels. Additional investigation with hypertonic saline administration or arginine stimulation testing may be needed to make this diagnosis. Plasma osmolality < 280 mOsm/kg and sodium levels < 135 mEq/L indicate primary polydipsia. Plasma osmolality > 280 mOsm/kg and sodium levels > 147 mEq/L suggest CDI or NDI. To then differentiate between CDI or NDI, copeptin levels should be measured. Copeptin ≤ 4.9 pmol/L occurs with CDI, while levels ≥ 21.4 pmol/L indicate NDI. If both plasma sodium and osmolality levels fall within the normal range, more specialized testing may be necessary. The water deprivation test has been the standard used to diagnose DI for many years; however, it has a low diagnostic accuracy of around only 70%. Alternatively, basal copeptin levels, hypertonic saline infusion, and the arginine stimulation testing all have significantly higher sensitivity and specificity. Copeptin levels taken before water deprivation or stimulation tests that exceed 21.4 pmol/L have a 100% sensitivity and specificity for the diagnosis of NDI [24]. The hypertonic saline test can be used to differentiate patients with primary polydipsia from patients with CDI with a 93% sensitivity and 100% specificity [24]. This test is performed by infusing 250 ml of 3% hypertonic saline over 15 minutes followed by infusing 0.15ml 3% saline/kg/minute with measurement of copeptin and sodium levels every 30 minutes. With the arginine stimulation testing, copeptin levels measured after the arginine infusion had a 92% sensitivity and 93% specificity distinguishing central DI from primary polydipsia [24]. Last, if CDI is diagnosed, magnetic resonance imaging (MRI) imaging is needed to investigate the etiology. The classic MRI finding in CDI is loss of the posterior pituitary bright spot, which represents depletion or absence of stored AVP [27]. However, the loss of a bright spot may also occur with age. The second most common MRI abnormality is thickening or enlargement of the pituitary stalk [26]. Pituitary stalk thickening can also occur with small craniopharyngiomas, lymphocytic hypophysitis, infiltrative disorders, autoimmune DI, and metastases, such as germinoma in children and young adults [26].

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4.4. Treatment

Desmopressin is the treatment of choice for CDI and gestational DI and can be administered orally, intranasally, subcutaneously, or intravenously. Oral desmopressin doses range from 0.05 mg to 0.8 mg (in divided doses) per day. The oral form has a lower potency than the nasal form because only about 5 percent is absorbed from the gut [24]. Nasal doses range from 10 mcg to 20 mcg per day. Intravenous or subcutaneous administration is used for acute DI which often occurs after TBI or neurosurgical surgery. Nephrogenic DI requires the discontinuation of all culprit medications and the use of a renal diet to prevent hypernatremia [28]. Treatment of primary polydipsia is aimed at regulating water intake with possible additional use of antipsychotic medications. Chronic alcohol consumption, particularly beer, with concurrent use of desmopressin is not recommended due to the risk of hyponatremia and alcohol-induced seizures. Patients with TBI and DI need attention to fluid intake, urine output, and sodium levels to maintain optimum electrolyte levels and serum tonicity.

5. Syndrome of Inappropriate Antidiuretic Hormone Secretion

5.1. Epidemiology in Traumatic Brain Injury

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is characterized by the excessive release or action of antidiuretic hormone (ADH), resulting in water retention and consequent hyponatremia. This disorder typically arises from injuries affecting the hypothalamus and posterior pituitary, where ADH is produced and secreted [29]. The renal tubules, particularly the collecting ducts, also contribute to this syndrome by responding inappropriately to ADH levels [30]. Furthermore, ectopic production of ADH, notably in cases of small-cell lung cancer, is a well-recognized cause of SIADH [31]. In the context of TBI, there are limited data regarding the specific sites of injury associated with SIADH. One case report suggests that chronic hyponatremia resulting from SIADH following TBI may reflect damage to the pituitary stalk or posterior pituitary, although no structural abnormalities were observed in computed tomography (CT) or MRI imaging in that case [32].

The frequency of SIADH in TBI patients remains inadequately addressed in existing literature. Chendrasekhar et al. found that among 310 patients with severe TBI, 32 patients (10%) were diagnosed with SIADH [33]. Other research has also identified SIADH as a significant contributor to hyponatremia in these patients. For example, Born et al. reported that in a cohort of 109 patients with severe TBI, 36 individuals (33%) presented with hyponatremia attributed to SIADH [25]. Similarly, Agha et al. studied 102 patients with moderate to severe TBI and found that 14 patients (13.7%) had hyponatremia, with 13 cases due to SIADH and one attributed to cerebral salt wasting syndrome (CSWS) [25].

In contrast, Lohani and Devkota observed a different incidence; among their 298 TBI patients, 50 (16.8%) presented with hyponatremia. Thirty-seven of these patients improved with sodium supplementation alone and did not meet the clinical criteria for SIADH; 13 required additional sodium retention therapy and were diagnosed with CSWS based on clinical symptoms. The authors highlighted a significant lack of clarity in the literature regarding the mechanisms underlying hyponatremia in TBI, citing variability in reported rates for SIADH, CSWS, and hypopituitarism. They recommended more research that incorporates evaluations of blood volume and hormonal assessments to elucidate the causes and frequencies of hyponatremia following TBI [35].

5.2. Clinical Presentation

The clinical presentation of SIADH in TBI patients depends on the type of trauma and the Na^+ concentration. In a study with 298 TBI patients, 50 individuals (16.8%) presented with hyponatremia during hospitalization. The incidence varied by TBI type; 47.9% of the patients had cerebral contusions, 34.8% had acute subdural hematomas, 25% had acute epidural hematomas, and 15.9% had chronic subdural hematomas. Most cases of hyponatremia occurred within three days of injury with a second peak observed after eight days. The average serum sodium level at the time of initial treatment was 133.7 ± 0.4 mEq/L. Although specific symptoms were not detailed, it was noted that

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hyponatremia can present with a spectrum of symptoms, ranging from mild manifestations, such as nausea and headaches, to severe complications, such as seizures and coma [36]. In addition, the study found that hyponatremia was associated with prolonged hospital stays and worse clinical outcomes in TBI patients. There was no significant difference in the initial Glasgow coma scale scores between patients who developed hyponatremia and patients who did not. The need to distinguish between SIADH and CSWS in TBI patients was emphasized, as treatment approaches differ. Among the 50 hyponatremic patients, 37 responded positively to sodium supplementation alone, while 13 required additional hydrocortisone treatment for persistent natriuresis. The precise mechanisms underlying hyponatremia following TBI remain unclear and are likely multifactorial, indicating a need for more studies incorporating blood volume and hormonal evaluations to better understand the etiology of hyponatremia in these patients [36].

5.3. Diagnosis

Diagnosing SIADH requires specific criteria that evaluate osmolality, urinary concentration, and volume status while excluding other potential causes. Key diagnostic criteria include reduced osmolality of extracellular fluid, i.e., a plasma osmolality below 275 mOsm/kg, and inappropriate urine concentration, i.e., urine osmolality above 100 mOsm/kg, despite normal renal function. Patients with SIADH are clinically euvolemic without fluid overload or dehydration and have elevated urinary sodium excretion (greater than 30 mEq/L) under normal salt and water intake. Supporting criteria for SIADH diagnosis include low serum uric acid levels (below 4 mg/dL), low blood urea nitrogen (BUN below 10 mg/dL), and uncorrected hyponatremia upon volume expansion, with improvement following fluid restriction. In some cases, a water load test may be used; abnormal results, i.e., excreting less than 80% of a 20 mL/kg water load within four hours, further support SIADH diagnosis. Elevated plasma AVP levels in the presence of hypotonicity and clinical euvolemia also support this diagnosis [37].

Excluding other causes of euvolemic hyponatremia, such as hypothyroidism, glucocorticoid deficiency, or medications that stimulate AVP release, is critical to confirm the diagnosis of SIADH. A fractional excretion of uric acid greater than 12% can further distinguish SIADH from hypovolemic hyponatremia. The diagnostic approach typically includes comprehensive laboratory testing, assessment of volume status, and a water restriction trial. In complex cases, measuring AVP or copeptin levels, along with conducting water load tests, may be necessary. In general, fulfilling core criteria in a euvolemic patient while ruling out other causes is sufficient for diagnosing SIADH [37].

5.4. Treatment

The incidence of hyponatremia in TBI patients varies across studies. According to a Moro study (2007), the incidence was 16.8%, with 50 out of 298 TBI patients presenting with hyponatremia. This condition was linked to longer hospital stays and poorer clinical outcomes. Among the hyponatremic patients, 37 improved with sodium supplementation alone, and 13 required additional treatment with hydrocortisone due to persistent natriuresis. The administration of hydrocortisone significantly decreased both sodium excretion and urine volume, indicating its effectiveness in managing hyponatremia [36].

Rajagopal et al. (2017) reported an incidence of hyponatremia of 13.2% in TBI patients (198 out of 1500). Traumatic subarachnoid hemorrhage was the most frequent abnormality on admission CT scans in patients who developed hyponatremia. The authors noted that early treatment with fludrocortisone significantly reduced the length of hospital stays for affected patients, and they proposed a management protocol for hyponatremia in TBI patients that used fludrocortisone early in cases accompanied by natriuresis. This approach aims to simplify treatment by eliminating the need to distinguish between SIADH and CSW, potentially streamlining patient care [38].

For all patients with SIADH, close monitoring of serum sodium is crucial, particularly during the first 24-48 hours of treatment, to prevent overly rapid corrections that could lead to osmotic demyelination syndrome. In general, the sodium correction rate should remain below 8-12 mEq/L within 24 hours or 18 mEq/L over 48 hours; in patients at high risk of osmotic demyelination, even

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slower correction rates (e.g., below 8 mEq/L in 24 hours) are recommended. During active correction with vaptans, fluid restriction is not advisable. Personalized treatment based on the severity of hyponatremia, symptoms, and patient risk factors is essential for safe and effective management [29].

6. Cerebral Salt Wasting Syndrome

Cerebral salt wasting syndrome (CSWS) is another important cause of hyponatremia in TBI patients and is distinct from SIADH [33]. While both conditions can lead to hyponatremia, CSW is characterized by hypovolemia, whereas SIADH typically presents with euvolemia or mild hypervolemia. Chendrasekhar et al. found that in 310 patients with severe TBI, 125 (40%) developed CSW, and 32 (10%) developed SIADH. This suggests that CSW may be more common than SIADH in TBI patients. Patients with CSW had significantly worse outcomes, including higher injury severity scores, longer hospital and ICU stays, more ventilator days, and lower survival rates than TBI patients without CSW [33]. Distinguishing between CSW and SIADH is crucial for appropriate treatment. Both disorders may initially be treated with hypertonic saline, but patients with CSWS often require additional volume expansion and sometimes mineralocorticoid therapy (e.g., fludrocortisone) for persistent natriuresis [39].

The management of patients with TBI and a sodium disorder can be challenging and it may be difficult to determine if the abnormal sodium levels reflect a clinical syndrome associated with TBI or reflect errors in management. Both hyponatremia and hypernatremia have been associated with poor outcomes in TBI patients. Hyponatremia is recognized as a significant independent factor associated with adverse neurological outcomes in TBI patients. In one study, hyponatremia occurred in 13.2% of TBI patients and was associated with higher 6-month mortality (23.5%) than patients with normal sodium levels (19.9%) [40]. A recent study identified an L-shaped relationship between sodium levels and in-hospital mortality in patients with TBI, with a critical threshold of 144.1 mEq/L. Patients with hypernatremia (sodium levels greater than 145 mEq/L) had a 2.17-fold increased risk of in-hospital death compared to those with normal or low sodium levels, even after controlling for potential confounding variables. This indicates that hypernatremia is independently linked to an increased risk of mortality in TBI patients, as discussed in the section on DI [41]. In addition, another study reported that 36.9% of patients with severe TBI developed hypernatremia, which was also independently associated with early mortality. The findings indicate that the mortality rates are high in patients with severe hypernatremia and indicate that clinicians must not overcorrect hyponatremia during the management of both SIADH and CSWS S [42].

7. Thirst in Traumatic Brain Injury

The initial evaluation of patients with TBI usually focuses on the level of consciousness and neurologic status or injuries/deficits. These injuries can cause psychiatric disorders which in turn can have important effects on sodium levels. This leads to the difficult question of whether the initial disorder involved thirst and fluid intake or abnormal antidiuretic hormone levels.

7.1. Site of Injury

Normal thirst responses depend on plasma osmolality and the oropharyngeal region that also has a role in the secretion of vasopressin [43,44]. Zimmerman et al. found that the subfornical organ (SFO) is involved in the anticipatory regulation of thirst, which allows drinking behavior to be modified [45]. In conditions such as polydipsia, the exact cause is still uncertain and is probably multifactorial. Available data suggest that it could be due to hypersensitivity to the effects of vasopressin, increases in the activity of dopamine, or even a defect in osmoregulation. Thirst-center stimulation in response to high dopamine levels with increased water intake consumption to counteract the effects of some psychotropic medications and changes in feedback regulation of the hypothalamic-pituitary axis in chronic polydipsia have also been described [46].

Studies have revealed changes in the osmotic set point for the release of vasopressin in patients with schizophrenia, and these are increased during acute episodes of psychosis. In addition,

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vasopressin dysfunction is present due to hippocampal impairment in the regulation of vasopressin and the hypothalamic-pituitary-adrenal axis, which suggests that hippocampal impairment in subjects who have TBIs are at risk of developing psychogenic polydipsia [47,48].

7.2. Epidemiology

The relation between thirst and changes in sodium has been studied, especially in those with psychogenic polydipsia, which includes a variety of psychiatric conditions, such as bipolar disorder, psychotic depression, and more commonly schizophrenia [46]. Patients with psychogenic polydipsia have a water intake greater than the kidneys' capacity to excrete it and drink up to 1 L/hr, resulting in hyponatremia due to a combination of poor solute consumption and excessive water consumption [49].

Mercier-Guidez et al. found that 11-20% of patients with chronic schizophrenia have psychogenic polydipsia with an intake of 5-15-L per day; these patients were symptomatic when sodium levels varied within 106 – 114 mEq/L [50]. Current data support the idea that TBI is a risk factor for schizophrenia, especially in patients with genetic susceptibilities to psychosis [51]. Conversely, adult patients who had TBI at an older age without any family history of psychiatric disorders can also develop schizophrenia [52]. A study done by Trivedi and his team found that hospitalized patients due to TBI have a 2.2 times greater likelihood of schizophrenia, especially in men. Greater risk is present in patients with bipolar disorders, anxiety disorders, personality disorders, substance abuse, intellectual disability, and young age [53].

7.3. Clinical Presentation

Symptoms suggesting hyponatremia in patients with psychiatric disorders include headache, fatigue, weakness, irritability, confusion, nausea, vomiting, and muscle cramps [54]. The presentation depends on how low the sodium level is and its rate of development. These symptoms are uncommon except in patients with an intake greater than 10 L daily, because they have reached their capacity to dilute urine and have developed a complete vasopressin suppression [55]. Attention should also be given to patients with urinary incontinence, including enuresis, as this can suggest polydipsia.

7.4. Diagnosis

Part of the workup when addressing abnormalities regarding excessive thirst requires to rule out other causes of polydipsia. Imaging studies are potentially useful since the thirst center can be affected by infiltrative diseases [56]. The context of the patient will suggest the possible etiology; for example, psychiatric patient behavior with increased fluid consumption due to delusional states or obsessive-compulsive tendency or to the use of psychotropic medications with anticholinergic side effects can lead to signs and symptoms of episodes with hyponatremia [54,57]. Hospitalized patients with alcoholism or eating disorders can use water to obtain pseudosatiety.

The water restriction test is the gold standard for the diagnosis of psychogenic polydipsia. In this test, a Posm higher than 295 mOsm/kg causes a maximal renal response to increased vasopressin levels. Before the test, patients usually have very diluted urine with an osmolality lower than 100 mOsm/kg and low values of vasopressin. After the test is done, patients have concentrated urine with osmolality greater than 600 mOsm/kg and high values of vasopressin [55].

7.5. Treatment

The onset and severity will guide the approach; patients with acute symptomatic and severe hyponatremia require treatment as described previously in the other sections. Fluid restriction should be guaranteed in patients with psychogenic polydipsia and hyponatremia [56]. Non-pharmacological management should include reinforcement schedules and fluid restriction. In monitored settings like hospitals or nursing homes management should include measuring diurnal weight and enforcing short fluid restriction periods (between 1 to 3 hours); acute increases in weight greater than 5 - 8 kg

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put the patient at risk of water intoxication [58]. Pharmacological medications can include antipsychotic medications, like risperidone and clozapine, and other medications, such as angiotensin-converting enzyme inhibitors, beta-blockers, and alpha-blockers, have demonstrated beneficial results in these patients [59–62]. However, their use has been reported in case studies, and no large trials or clear guidelines are available. Long- term management requires behavioral management and close vigilance by health professionals due to its relapsing behavior.

Important laboratory results for the clinical disorders associated with abnormal sodium levels in patients with TBI are summarized in the Table 1.

Table 1. Laboratory results and characteristics of water balance disorders related to traumatic brain injury.

Condition	Key features	Laboratory results	Correlation with traumatic brain injury
Diabetes insipidus	Central DI: Deficiency of ADH due to hypothalamic or pituitary damage. Nephrogenic DI: Renal insensitivity to ADH.	Hypernatremia (serum sodium >145 mEq/L); Elevated serum osmolality (>295 mOsm/kg); Low urine osmolality (<300 mOsm/kg); Low copeptin levels (<5 pmol/L in central DI)	Common post-TBI, often due to damage affecting the hypothalamic-pituitary axis, leading to impaired ADH secretion.
Syndrome of inappropriate antidiuretic hormone secretion	Inappropriate secretion of ADH: Water retention and dilutional hyponatremia.	Hyponatremia (serum sodium <135 mEq/L); Inappropriately concentrated urine (urine osmolality >100 mOsm/kg); Low serum osmolality (<275 mOsm/kg); Elevated copeptin levels (>10 pmol/L)	Commonly occurs TBI, associated with direct brain injury
Cerebral salt wasting	Excessive renal sodium excretion: Hypovolemia and hyponatremia due to natriuresis.	Hyponatremia (serum sodium <135 mEq/L); Inappropriately elevated urine sodium concentration (>20 mEq/L); High urine osmolality (>300 mOsm/kg); Normal to elevated copeptin levels (5-10 pmol/L)	Frequently associated with TBI and neurosurgery; often a response to increased intracranial pressure and resultant changes in fluid balance.
Primary polydipsia	Psychogenic condition: Excessive water intake, despite normal renal function.	Low urine osmolality (<300 mOsm/kg); Serum sodium may be normal or mildly low; Low to normal copeptin levels (<5 pmol/L)	Can arise after TBI, particularly in patients with psychological stress or brain injuries affecting behavior, usually a separate entity from ADH dysregulation.

ADH: Antidiuretic hormone; DI: Diabetes insipidus; TBI: Traumatic brain injury.

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8. Discussion

Patients with TBIs have complex presentations that depend on the type and severity of the injury and other trauma-related injuries. They likely will need evaluation by a neurosurgeon, a trauma surgeon, a critical care specialist, and a neurologist. The initial injury may be complicated by the development of additional intracranial bleeding, intracranial hypertension, decreased cerebral perfusion, and electrolyte abnormalities. These patients are at risk to develop both hyponatremia secondary to SIADH secretion and CSWS and hypernatremia secondary to diabetes insipidus. They may also have behavioral abnormalities that interfere with their treatment. This could represent new onset schizophrenia or the effects of brain contusion. These abnormalities can lead to excessive water ingestion or inadequate water ingestion. The clinician should expect these patients to have abnormalities in electrolytes and order serial measurements of sodium. Patients with increases or decreases in sodium need a more comprehensive clinical and laboratory evaluation. The clinician needs to decide if the patient is euvolemic, hypovolemic, or hypervolemic. Urine output and urine electrolytes should be measured, and thyroid and adrenal function tests should be obtained. Patients with hyponatremia and clinical symptoms attributable to this hyponatremia should have serum sodium levels corrected. This should be done cautiously to avoid the possibility of osmotic demyelination. Patients with hypernatremia will need volume expansion. Patients with abnormal thirst may need fluid restriction or scheduled fluid administration. Dysnatremia and fluid status are ongoing concerns and need frequent reevaluation.

9. Conclusions

Abnormal sodium concentrations occur frequently in patients with TBI. These electrolyte disorders contribute to both morbidity and mortality and will need careful evaluation and frequent follow-up. It may be difficult to determine if the abnormal sodium concentration is contributing to the clinical presentation, but that possibility should be an ongoing consideration with regular efforts to maintain sodium levels in the normal range.

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References

1. Quinones-Ossa G A, Padilla-Zambrano H, Pal R, Ghosh A, Moscote-Salazar L R, Kiran Kumar V A, Agrawal A. Biomarkers in acute brain trauma: A narrative review. Journal of Acute Disease 8(1):p 1-6, January 2019. | DOI: 10.4103/2221-6189.250370.
2. McDonald SJ, Obrien TJ, Shultz SR.. Biomarkers add value to traumatic brain injury prognosis. The Lancet Neurology 2022; 21 (9): 761 – 763.
3. Elias J, Sutherland E, Kennedy E. Concussion Management in Older People: A Scoping Review. J Head Trauma Rehabil. 2024 Jul-Aug 01;39(4):293-303. doi: 10.1097/HTR.0000000000000933.
4. Moore S, Musgrave C, Sandler J, Bradley B, Jones JRA. Early intervention treatment in the first 2 weeks following concussion in adults: A systematic review of randomised controlled trials. Phys Ther Sport. 2024 Jan; 65:59-73. doi: 10.1016/j.ptsp.2023.11.005.
5. American College of Surgeons. Trauma Programs. Best Practices Guidelines. Management of Traumatic Brain Injury. https://www.facs.org/quality-programs/trauma/quality/best-practices-guidelines/.
6. Smith M, Baltazar GA, Pate A, Akella K, Chendrasekhar A. Hyponatremia on Initial Presentation Correlates with Suboptimal Outcomes after Traumatic Brain Injury. Am Surg. 2017 Apr 1;83(4): e126-128. PMID: 28424116.

7. The Centers for Disease Control. Traumatic Brain Injury-related Deaths by Age Group, Sex, and Mechanism of Injury. https://www.cdc.gov/traumaticbraininjury/pdf/tbi-surveillance-report-2018-2019-508.pdf- accessed 10-28-2024.
8. Flores-Sandoval C, MacKenzie HM, McIntyre A, Sait M, Teasell R, Bateman EA. Mortality and discharge disposition among older adults with moderate to severe traumatic brain injury. Arch Gerontol Geriatr. 2024 Oct; 125:105488. doi: 10.1016/j.archger.2024.105488.
9. The International Mission for Prognosis and Analysis of Clinical Trials (IMPACT). http://www.tbi-impact.org/?p=impact/calc
10. CRASH. Head injury prognosis. https://crash.lshtm.ac.uk/Risk%20calculator/index.html.
11. Eagle SR, Nwachuku E, Elmer J, Deng H, Okonkwo DO, Pease M. Performance of CRASH and IMPACT Prognostic Models for Traumatic Brain Injury at 12 and 24 Months Post-Injury. Neurotrauma Rep. 2023 Mar 1;4(1):118-123. doi: 10.1089/neur.2022.0082.
12. Iderdar Y, Arraji M, Wachami NA, Guennouni M, Boumendil K, Mourajid Y, Elkhoudri N, Saad E, Chahboune M. Predictors of outcomes 3 to 12 months after traumatic brain injury: a systematic review and meta-analysis. Osong Public Health Res Perspect. 2024 Feb;15(1):3-17. doi: 10.24171/j.phrp.2023.0288.
13. Steyerberg EW, Mushkudiani N, Perel P, Butcher I, Lu J, McHugh GS, Murray GD, Marmarou A, Roberts I, Habbema JD, Maas AI. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. PLoS Med. 2008 Aug 5;5(8): e165; discussion e165. doi: 10.1371/journal.pmed.0050165.
14. Zerbe RL, Robertson GL. Osmoregulation of thirst and vasopressin secretion in human subjects: effect of various solutes. *Am J Physiol*. Jun 1983;244(6):E607-14. doi:10.1152/ajpendo.1983.244.6.E607
15. 15. Humes HD, Narins RG, Brenner BM. Disorders of water balance. *Hosp Pract*. Mar 1979;14(3):133-45. doi:10.1080/21548331.1979.11707506
16. 16. Robertson GL. Thirst and vasopressin function in normal and disordered states of water balance. *J Lab Clin Med*. Mar 1983;101(3):351-71.
17. Zerbe RL, Miller JZ, Robertson GL. The reproducibility and heritability of individual differences in osmoregulatory function in normal human subjects. *J Lab Clin Med*. Jan 1991;117(1):51-9.
18. Buonocore CM, Robinson AG. The diagnosis and management of diabetes insipidus during medical emergencies. *Endocrinol Metab Clin North Am*. Jun 1993;22(2):411-23.
19. Gardiner TW, Verbalis JG, Stricker EM. Impaired secretion of vasopressin and oxytocin in rats after lesions of nucleus medianus. *Am J Physiol*. Dec 1985;249(6 Pt 2):R681-8. doi:10.1152/ajpregu.1985.249.6.R681
20. Verbalis JG. How does the brain sense osmolality? *J Am Soc Nephrol*. Dec 2007;18(12):3056-9. doi:10.1681/ASN.2007070825
21. Smith D, McKenna K, Moore K, et al. Baroregulation of vasopressin release in adipsic diabetes insipidus. *J Clin Endocrinol Metab*. Oct 2002;87(10):4564-8. doi:10.1210/jc.2002-020090
22. Cash A, Theus MH. Mechanisms of Blood-Brain Barrier Dysfunction in Traumatic Brain Injury. Int J Mol Sci. 2020 May 8;21(9):3344. doi: 10.3390/ijms21093344. PMID: 32397302; PMCID: PMC7246537.
23. Tomkins M, Lawless S, Martin-Grace J, Sherlock M, Thompson CJ. Diagnosis and Management of Central Diabetes Insipidus in Adults. *Journal of Clinical Endocrinology & Metabolism*. 2022;107(10):2701. doi:10.1210/clinem/dgac381
24. Christ-Crain M, Winzeler B, Refardt J. Diagnosis and management of diabetes insipidus for the internist: an update. *Journal of internal medicine*. 2021;290(1):73-87. doi:10.1111/joim.13261
25. Agha A, Thornton E, O'Kelly P, Tormey W, Phillips J, Thompson CJ. Posterior pituitary dysfunction after traumatic brain injury. *J Clin Endocrinol Metab*. 2004;89(12):5987-5992. doi:10.1210/jc.2004-1058
26. Capatina C, Paluzzi A, Mitchell R, Karavitaki N. Diabetes Insipidus after Traumatic Brain Injury. *Journal of Clinical Medicine*. 2015; 4(7):1448-1462. https://doi.org/10.3390/jcm4071448
27. Garrahy A, Moran C, Thompson CJ. Diagnosis and management of central diabetes insipidus in adults. *Clin Endocrinol (Oxf)*. 2019;90(1):23-30. doi:10.1111/cen.13866
28. Mutter CM, Smith T, Menze O, Zakharia M, Nguyen H. Diabetes Insipidus: Pathogenesis, Diagnosis, and Clinical Management. *Cureus*. 2021;13(2):e13523. Published 2021 Feb 23. doi:10.7759/cureus.13523
29. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, Thompson CJ. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013 Oct;126(10 Suppl 1):S1-42. doi: 10.1016/j.amjmed.2013.07.006. PMID: 24074529.
30. Martin-Grace J, Tomkins M, O'Reilly MW, Thompson CJ, Sherlock M. Approach to the Patient: Hyponatremia and the Syndrome of Inappropriate Antidiuresis (SIAD). J Clin Endocrinol Metab. 2022 Jul 14;107(8):2362-2376. doi: 10.1210/clinem/dgac245. PMID: 35511757; PMCID: PMC9282351.
31. Yasir M, Mechanic OJ. Syndrome of Inappropriate Antidiuretic Hormone Secretion. 2023 Mar 6. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 29939554.
32. Dick M, Catford SR, Kumareswaran K, Hamblin PS, Topliss DJ. Persistent syndrome of inappropriate antidiuretic hormone secretion following traumatic brain injury. Endocrinol Diabetes Metab Case Rep. 2015;2015:150070. doi: 10.1530/EDM-15-0070. Epub 2015 Aug 27. PMID: 26527077; PMCID: PMC4626642.

33. Chendrasekhar A, Chow PT, Cohen D, Akella K, Vadali V, Bapatla A, Patwari J, Rubinshteyn V, Harris L. Cerebral Salt Wasting in Traumatic Brain Injury Is Associated with Increased Morbidity and Mortality. Neuropsychiatr Dis Treat. 2020 Mar 25;16:801-806. doi: 10.2147/NDT.S233389. PMID: 32273706; PMCID: PMC7104213.
34. Born JD, Hans P, Smitz S, Legros JJ, Kay S. Syndrome of inappropriate secretion of antidiuretic hormone after severe head injury. Surg Neurol. 1985 Apr;23(4):383-7. doi: 10.1016/0090-3019(85)90212-5. PMID: 3975827.
35. Lohani S, Devkota UP. Hyponatremia in patients with traumatic brain injury: etiology, incidence, and severity correlation. World Neurosurg. 2011 Sep-Oct;76(3-4):355-60. doi: 10.1016/j.wneu.2011.03.042. PMID: 21986437.
36. Moro N, Katayama Y, Igarashi T, Mori T, Kawamata T, Kojima J. Hyponatremia in patients with traumatic brain injury: incidence, mechanism, and response to sodium supplementation or retention therapy with hydrocortisone. Surg Neurol. 2007 Oct;68(4):387-93. doi: 10.1016/j.surneu.2006.11.052. PMID: 17905062.
37. Pliquett RU, Obermüller N. Endocrine Testing for the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH). 2022 Dec 22. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J, Kalra S, Kaltsas G, Kapoor N, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, New M, Purnell J, Sahay R, Shah AS, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–. PMID: 25905283.
38. Rajagopal R, Swaminathan G, Nair S, Joseph M. Hyponatremia in Traumatic Brain Injury: A Practical Management Protocol. World Neurosurg. 2017 Dec;108:529-533. doi: 10.1016/j.wneu.2017.09.013. Epub 2017 Sep 9. PMID: 28899834.
39. Daghmouri MA, Ouesleti M, Touati MA, Faten O, Zakhama S, Rebai L. Cerebral Salt Wasting Syndrome Caused by Severe Traumatic Brain Injury in a Pediatric Patient and Review of the Literature. Case Rep Crit Care. 2021 Oct 22;2021:6679279. doi: 10.1155/2021/6679279. PMID: 34721906; PMCID: PMC8556096.
40. Jung E, Ryu HH, Ryu SJ, Kong SY. Risk of pre-existing hyponatremia and mortality in patients with traumatic brain injury across age groups. Heliyon. 2022 Sep 28;8(10):e10814. doi: 10.1016/j.heliyon.2022.e10814. PMID: 36211992; PMCID: PMC9539780.
41. Wang X, Li X, Sun J, Wang M, Lang W, Xu X. Relationship between sodium level and in-hospital mortality in traumatic brain injury patients of MIMIC IV database. Front Neurol. 2024 Mar 18;15:1349710. doi: 10.3389/fneur.2024.1349710. PMID: 38562424; PMCID: PMC10982354.
42. Vedantam A, Robertson CS, Gopinath SP. Morbidity and mortality associated with hypernatremia in patients with severe traumatic brain injury. Neurosurg Focus. 2017 Nov;43(5):E2. doi: 10.3171/2017.7.FOCUS17418. PMID: 29088954.
43. Figaro MK, Mack GW. Regulation of fluid intake in dehydrated humans: role of oropharyngeal stimulation. Am J Physiol. 1997 Jun;272(6 Pt 2):R1740-1746.
44. Armstrong LE, Muñoz CX, Armstrong EM. Distinguishing Low and High Water Consumers—A Paradigm of Disease Risk. Nutrients. 2020 Mar 23;12(3):858.
45. Zimmerman CA, Lin YC, Leib DE, Guo L, Huey EL, Daly GE, et al. Thirst neurons anticipate the homeostatic consequences of eating and drinking. Nature. 2016 Sep 29;537(7622):680–4.
46. Bhatia M, Goyal A, Saha R, Doval N. Psychogenic Polydipsia – Management Challenges. Shanghai Arch Psychiatry. 2017 Jun 25;29(3):180.
47. Goldman MB. The mechanism of life-threatening water imbalance in schizophrenia and its relationship to the underlying psychiatric illness. Brain Res Rev. 2009 Oct;61(2):210–20.
48. Zafonte RD, Watanabe TK, Mann NR, Ko DH. Psychogenic polydipsia after traumatic brain injury. A case report. Am J Phys Med Rehabil. 1997;76(3):246–8.
49. Buffington MA, Abreo K. Hyponatremia: A Review. J Intensive Care Med. 2016 May 1;31(4):223–36.
50. Mercier-Guidez E, Loas G. Polydipsia and water intoxication in 353 psychiatric inpatients: an epidemiological and psychopathological study. Eur Psychiatry J Assoc Eur Psychiatr. 2000 Aug;15(5):306–11.
51. Molloy C, Conroy RM, Cotter DR, Cannon M. Is Traumatic Brain Injury A Risk Factor for Schizophrenia? A Meta-Analysis of Case-Controlled Population-Based Studies. Schizophr Bull. 2011 Nov 1; 37 (6): 1104–10.
52. Nkemjika S, Olayinka O, Atolagbe A, Begum G, Perera P, Oladeji O, et al. Traumatic brain Injury related schizophrenia in individuals without family history: A case series. J Natl Med Assoc. 2022 Apr 1; 114 (2): 207–10.
53. Trivedi C, Reddy P, Rizvi A, Husain K, Brown K, Mansuri Z, et al. Traumatic Brain Injury and Risk of Schizophrenia and Other Non-mood Psychotic Disorders: Findings From a Large Inpatient Database in the United States. Schizophr Bull. 2024 Jul 1; 50 (4): 924–30.
54. Siegel AJ. Hyponatremia in psychiatric patients: update on evaluation and management. Harv Rev Psychiatry. 2008;16(1):13–24.

55. Dundas B, Harris M, Narasimhan M. Psychogenic polydipsia review: etiology, differential, and treatment. Curr Psychiatry Rep. 2007 Jun;9(3):236–41.
56. Sahay M, Sahay R. Hyponatremia: A practical approach. Indian J Endocrinol Metab. 2014 Dec;18(6):760.
57. Illowsky BP, Kirch DG. Polydipsia and hyponatremia in psychiatric patients. Am J Psychiatry. 1988 Jun;145(6):675–83.
58. Ahmadi L, Goldman MB. Primary polydipsia: Update. Best Pract Res Clin Endocrinol Metab. 2020 Sep;34(5):101469.
59. Verghese C, de Leon J, Josiassen RC. Problems and progress in the diagnosis and treatment of polydipsia and hyponatremia. Schizophr Bull. 1996;22(3):455–64.
60. Greendyke RM, Bernhardt AJ, Tasbas HE, Lewandowski KS. Polydipsia in chronic psychiatric patients: therapeutic trials of clonidine and enalapril. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 1998 Apr;18(4):272–81.
61. Kruse D, Pantelis C, Rudd R, Quek J, Herbert P, McKinley M. Treatment of psychogenic polydipsia: comparison of risperidone and olanzapine, and the effects of an adjunctive angiotensin-II receptor blocking drug (irbesartan). Aust N Z J Psychiatry. 2001 Feb; 35 (1): 65–8.
62. Shanmugalingam A. Use of clozapine to treat psychogenic polydipsia in schizoaffective disorder—A case report. Psychiatry Res Case Rep. 2022 Dec 1; 1 (2): 100062.