Chapter 1
Epidemiology and Significance of Hyponatremia

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Introduction

Hyponatremia is a common electrolyte disturbance encountered within different clinical scenarios and populations. Its incidence and prevalence is influenced by the degree of hyponatremia and the available sodium measurements. We will assess the presence of hyponatremia along with its etiology and its impact on morbidity and mortality within the select literature.

Population Studies in Various Clinical Settings

Hospital and Community Settings

Hyponatremia is commonly encountered in the hospitalized patient and, to a lesser degree, within the community. In one of the largest comprehensive studies, Hawkins evaluated 120,137 Singapore patients for the prevalence of hyponatremia in both the hospital and community [1]. Within the community, he noted hyponatremia in about 4–7 % of the patients presenting to a primary care clinic. A similar number of hyponatremic patients [2] are seen in the emergency department (ED), but one-third of these patients (1.4 % of total) have a plasma sodium <125 mEq/L which is ten times higher than what Hawkins reported in the community. This higher frequency

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Table 1.1 Hyponatremia within the general population in community and hospital settings determined by sodium levels used to define hyponatremia

Population studies				
Reference	Sodium	Frequency (%)	Sample size	Study type
Community				
Hawkins [1]	<136	7.2	24,027	R
Hawkins [1]	<135	4.3	24,027	R
Hawkins [1]	<126	0.14	24,027	R
Emergency department				
Lee [2]	<134	3.8	3,784	P
Lee [2]	<125	1.4	3,784	P
Hospital				
Hawkins [1]	<136	42.6	43,249	R
Hoorn [3]	<136	30	2,907	P
Anderson [4]	<130	2.5	Unknown	P
Hawkins [1]	<126	6	43,249	R
Hoorn [3]	≤125	3	2,907	P
Intensive care unit				
Hoorn [3]	<136	38	2,907	P
DeVita [5]	≤134	29.6	98	P
Funk [6]	<125	1.2	151,486	R
Hoorn [3]	≤125	2	2,907	P

R retrospective study, *P* prospective study

of moderate hyponatremia correlates with a sicker population as two-thirds of the patients in the ED have hypovolemic hyponatremia due to gastrointestinal losses.

In the hospital setting, hyponatremia is more prevalent and severe. A number of studies (see Table 1.1) show that about 30–40 % of all hospitalized patients have some degree of mild hyponatremia [1, 3]. These studies suggest that mild hyponatremia is common in hospitalized patients, but there is a question of the actual incidence, as sodium measurements are missing in as many as half of the patients that may be at risk for developing hyponatremia [4].

Even with this discrepancy in sodium measurements, moderate hyponatremia is encountered in 2–6 % of patients depending on the cutoff level [1, 3, 4, 7]. About half of these patients have hyponatremia on admission while the other half developed it during their hospitalization [1]. When it comes to severe hyponatremia, Hawkins [1] noted that 1.2 % of all patients had serum sodium <116 mmol/L while Anderson et al. and others have reported a plasma sodium <120 mEq/L in about 0.5 % of the patients on admission [4, 7, 8]. Although this prevalence is low, again, it is about ten times higher than what is seen in the community [1].

The frequency of hyponatremia in the intensive care unit (ICU) is similar to the general hospital population (see Table 1.1) with 30–40 % having some degree of mild hyponatremia [5, 6, 9]. Severe hyponatremia in the ICU is similar to what is seen in the general hospital setting [3].

The etiology of hyponatremia varies depending on the clinical setting. Those presenting to an ED had mostly hypovolemic hyponatremia. As one transitions to admitted patients, the etiology changes to include a larger number of patients with drug-induced hyponatremia [3]. In the ICU setting and with severe hyponatremia, the causes now include a high level of antidiuretic hormone (ADH) secretion, which may or may not be appropriate, along with more hypotonic fluid administration and subsequent hospital acquired hyponatremia [3]. The number of patients that develop symptoms as a result of iatrogenic hyponatremia has been reported as high as 36 % with 19 % of these patients dying [3].

Hyponatremia is associated with adverse outcomes, and a delay in treatment can result in increased adverse events. Hoorn et al. [3] specifically examined hospital-acquired hyponatremia and found patients had a longer time to initiation of treatment and, consequently, a longer hospital stay. Hyponatremia is also considered to be a marker for underlying illness, and the severity of the hyponatremia may parallel the magnitude of the underlying disease which impacts mortality. A prospective study [10] of acutely hospitalized elderly patients with mild hyponatremia found no difference in 3-month mortality, compared to normonatremic patients, once adjusted for comorbidities. However, for moderate hyponatremia, in-hospital mortality was twice as high (16 %) compared to those without admission hyponatremia [7]. Similarly, Gill et al. [11] showed a threefold higher (27 %) mortality associated with severe hyponatremia (serum sodium <125 mmol/L). Acquired hyponatremia in the ICU also doubles the risk of mortality [9]; ICU-acquired hyponatremia has been associated with an 18 % ICU mortality compared to 9 % in those who always had normal sodium, and these patients also had higher hospital mortality (28 % vs. 16 %). Waikar et al. [8] evaluated patients to see if an improvement of hyponatremia translated to improved outcomes and noted that mortality (in hospital, 1-year and 5-year) was slightly better for those that corrected their hyponatremia during the hospitalization compared to those with persistent hyponatremia, though it was best for those who were always normonatremic.

Hyponatremia increases mortality risk but the exact relationship is unclear. Mortality may be attributed to the underlying disease, and the severity of hyponatremia may indicate progression of disease and result in worse outcomes. Hyponatremia can cause harm and present with symptoms such as confusion, nausea, vomiting, or seizures and can result in direct central nervous system (CNS) injury and death if not recognized and treated in time.

Postoperative

Healthy individuals can develop hyponatremia postoperatively with detrimental outcomes as reported by Arieff [12] in his study of 15 previously healthy women whom he encountered during a 10-year time span. The women underwent elective surgery with average preoperative serum sodium of 138 mmol/L and subsequently developed seizures and respiratory arrest postoperatively with average serum

Table 1.2 Hyponatremia within the postoperative patients

Postoperative				
Reference	Sodium	Frequency (%)	Sample size	Study type
Caramelo [14]	<135	12.5	112	P
Chung [15]	<130	4.4	1,088	P
Herrod [16]	<130	2.9	1,383	P
Madiba [17]	<130	2.2	71	P
Widjicks [13]	<130	0.004	290,815	R

R retrospective study, *P* prospective study

sodium of 108 mmol/L. The postoperative fluid balance was positive 7.5 L, and the urine sodium and osmolality suggested the syndrome of inappropriate antidiuretic hormone (SIADH). Hyponatremia was suspected as the cause of symptoms in one-third of the women, prompting early treatment. The other two-thirds had a delay of treatment of about 16 h mainly due to lack of recognition of symptomatic hyponatremia. Four of these women died and nine remained in permanent vegetative state. The other two patients recovered with significant neurological deficits.

Following Arieff's report, a large retrospective study at the Mayo clinic [13] examined the incidence of postoperative hyponatremia in 290,815 procedures on women over a 16-year period. They identified 1,791 women with cardiopulmonary resuscitation, new-onset seizures, central pontine myelinolysis, or metabolic encephalopathy. Only 11 patients within this subgroup had hyponatremia indicating an overall percentage of only 0.004 %. Interestingly, none of the 1,498 women with cardiac or respiratory arrest had hyponatremia.

Since then, there have been a number of prospective studies (see Table 1.2) looking at hyponatremia in the postoperative setting. One study [15] found 4.4 % of patients with a plasma sodium <130 mEq/L. Most of these patients were normovolemic, and 94 % were being given hypotonic fluids when they developed hyponatremia. Similarly, in a study by Madiba et al. [17] 2.2 % of 71 patients had a serum sodium <130 mmol/L, although one-fourth had documented hyperglycemia. None of the patients had a serum sodium less than 110 mmol/L and none developed neurological symptoms. Most episodes of hyponatremia occurred in normovolemic patients receiving hypotonic fluids.

Hyponatremia is associated with the use of hypotonic fluids in patients undergoing transurethral resection of the prostate (TURP) for the treatment of symptomatic benign prostatic hyperplasia (BPH). Traditional treatment has used a monopolar TURP which requires a nonconductive, electrolyte-free irrigation fluid (glycine, sorbitol, or mannitol). Occurrences of symptomatic hyponatremia (serum sodium <125 mmol/L) have been reported in about 2–7 % of patients undergoing this procedure. However, the use of bipolar transurethral resection, which uses isotonic saline, has minimized this rate to almost zero [18]. Similar accounts have been documented in female patients undergoing operative hysteroscopy, which require large amounts of a distention medium during surgery [19].

Table 1.3 Hyponatremia in the elderly in various clinical settings determined by sodium levels used to define hyponatremia

Elderly Patients				
Reference	Sodium	Frequency (%)	Sample size	Study type
Population Study, 55+				
Sajadieh [21]	≤137	9.2	671	P
Hoorn [22]	<136	7.7	5,208	P
Sajadieh [21]	≤134	2.1	671	P
Nursing home, 60+				
Miller [23]	≤135	18	119	R
Hawkins [1]	<135	18.2	51,659	R
Hospital, 65+				
Frenkel [10]	<135	34.3	895	P
Anpalahan [24]	<135	25	172	P
Byatt [25]	<130	6.9	929	P
Terzian [7]	<130	3.5	4,123	R
Shapiro [26]	≤125	6.2	86	P
Terzian [7]	<120	0.8	4,123	R
Hawkins [1]	<116	0.44	51,659	R

R retrospective study, *P* prospective study

Although hypotonic fluids have been implicated as a possible cause of hyponatremia in postoperative patients, several studies have rigorously examined this hypothesis and found that patients who developed hyponatremia are not necessarily given more hypotonic fluids than their normonatremic counterparts but, rather, these patients retain more water [14, 16, 20]. The results of these studies are consistent with transient SIADH due to pain and/or drugs which explains why patients given isotonic fluids also retain water [20].

In summary, the incidence of postoperative hyponatremia seems to be small and a large portion of the hyponatremia develops as a consequence of SIADH and administration of hypotonic fluid, although isotonic fluid may also cause hyponatremia in the setting of elevated ADH.

Elderly

Various articles reported on the incidence of hyponatremia in the elderly but used inconsistent definitions and within differing age distributions (see Table 1.3). As a consequence, there are mixed results in terms of incidence, prevalence, and its impact on morbidity and mortality. The etiology and contributing factors are also important for better management and treatment. The chronicity and acuity have not been elucidated in these studies and may play a role in terms of symptoms and outcome.

Two large population-based studies evaluated patients aged 55 and older and showed a frequency of mild hyponatremia of less than 10 % [21, 22]. There was a higher frequency of diuretic use in the hyponatremic groups compared to the controls [21, 22]. Miller et al. [23] looked at hyponatremia in a nursing home population, 60 and older, via a retrospective record review and prospective study. They found 18 % of patients had a serum sodium $\leq$135 mEq/L, the same as what Hawkins' [1] found in his older than 60 group, compared to an age-control ambulatory group of 8 %. When they examined all the sodium measurements for the past 12 months, 53 % of the patients had at least one episode of hyponatremia, and it was more common in a variety of CNS disorders and in 100 % of those with spinal cord injury. Surprisingly, no difference was noted between the hyponatremic and normonatremic groups in terms of cardiovascular disease, diabetes, or diuretic use. They also prospectively evaluated 23 hyponatremic patients with a water loading test and found abnormal water handling in 18 patients with an impaired urinary diluting ability compared to healthy controls consistent with SIADH.

Other studies have looked at patients age 65 and older in the hospital setting with varying severity of hyponatremia. Prospective studies found one-fourth [24] to one-third [10] of patients have mild hyponatremia (serum sodium <135 mmol/L) with SIADH as the etiology in half of the cases [24].

Moderate hyponatremia (serum sodium <130 mmol/L) is also present in a significant number of elderly patients. A study of 1,000 consecutive geriatric (65 years old and older) admissions [25] found hyponatremia in 7 % of all patients. Notably, half of the hyponatremic patients were receiving diuretics. A large retrospective study [7] noted a serum sodium <130 mmol/L in 3.5 % of the patients with women having almost twice the incidence (4.6 % vs. 2.6 %). A prospective, observational study [26] found 6 % of hospitalized elderly patients with a serum sodium $\leq$125 mEq/L. They found no increase of hyponatremia with age, but there were again twice as many females as males (8 % vs. 4 %) though women were nearly twice as likely to use thiazides and antidepressants compared to men. The most common contributing cause of hyponatremia was SIADH in about 60 % of the patients but multifactorial in half of the patients. Severe hyponatremia is uncommon in this population, seen in <1% of all patients [7] older than age 60.

Hyponatremia can contribute to falls and fractures in the elderly. Gankam Kengne et al. [27] performed a case control study of 513 cases with bone fractures after incidental falls in ambulatory patients 65 and older. They noted a serum sodium <135 mEq/L in 13 % vs. 3.9 % of controls. These were admissions for bone fractures. Hyponatremia was mild and asymptomatic and generally due to drugs (36 % diuretics, 17 % SSRI's) or SIADH (37 %). Hyponatremia was associated with falls in the ambulatory elderly with an odds ratio of 4.2 (adjusted). In the Rotterdam Study [22], hyponatremic elderly patients had more falls (24 % vs. 16 % for normonatremic patients) at baseline, and they had an increased risk of vertebral fractures and incident non-vertebral fractures even though there was no association with a lower bone mineral density in this group.

The cause of hyponatremia in the elderly population is often multifactorial. SIADH is the single leading cause of hyponatremia in 37 % to 78 % of the cases

[23, 24, 26, 27]. This is confounded by the use of diuretics in this population which ranges from 15 % to 43 % [21, 22, 25, 27]. Older age can also be a factor in the development of hyponatremia which may be due to a reduced capacity of the kidneys to handle free water [23]. Women have a higher incidence of hyponatremia in this group, but this is also associated with a higher use of drugs that impact the kidney's diluting ability or may cause SIADH.

Morbidity and mortality is significant in this population, and hyponatremia may be a contributing factor but the reports are mixed. There are studies that show an increase in adverse effects as hyponatremia worsens [21] along with a twofold increase in mortality [7, 22] and increase in falls [27], but other reports show no association between hyponatremia and increased mortality [10, 23, 25] even when severe [26].

Pediatrics

Hyponatremia within the pediatric population can result in subsequent neurological complications due to brain edema. It is seen in CNS and lung pathology and in gastrointestinal losses, and is also iatrogenic due to fluid administration in the hospitalized child. Some report hyponatremia (serum sodium <135 mEq/L) in one-fourth of hospitalized children [28]. Hoorn et al. [29] evaluated data from all children who presented to the ED in a 3-month period and noted a plasma sodium <136 mmol/L in 8.2 % of the 1,586 patients with at least one sodium measurement. About 70 % had hyponatremia on admission, and the rest developed it during their hospital stay. During a case-controlled portion of the study, they noted that children with hospital-acquired hyponatremia received almost as twice as much electrolyte-free water and total volume than their controls. Symptoms were mild; mainly headache and vomiting, but two children had significant neurological sequela. One child with a seizure disorder developed seizures during the hyponatremic episode, and another child had a cardiac arrest and died. Post-mortem analysis revealed brain edema.

These studies show that hyponatremia is common in the pediatric population and more pronounced when more electrolyte-free water is given.

Gender

Arieff's [12] study, discussed above, detailed the detrimental outcomes of 15 previously healthy women with hyponatremia in the postoperative setting. This led various authors to examine the role of female sex in the development of hyponatremia. Some studies show a relationship between female sex and the development of hyponatremia [2, 12, 20, 26] while others do not support this association [13, 30, 31]. One prospective study found a twofold higher frequency

of hyponatremia in women than in men, but the women were using twice as many diuretics and selective serotonin uptake inhibitors (SSRI's) than males. Nevertheless, it is still unclear why women develop hyponatremia more frequently than men, but it may be that there are confounding factors such as hormones, medications that cause hyponatremia, and a low body mass index (BMI). In marathon runners, female sex may be a possible risk factor, but this is also confounded by a lower BMI and a longer race time that may lead to more fluid consumption [30].

Specific Conditions

Central Nervous System Disorders

Hyponatremia is known to occur with various CNS abnormalities, and the etiology can differ depending on the underlying disease.

Sherlock et al. [32] reported on hyponatremia in various neurosurgical patients and found an incidence of 11 % for a plasma sodium <130 mmol/L in this retrospective study of 1,698 patients. Hyponatremia was present in 6.3 % of patients with pituitary disorders, 20 % with subarachnoid hemorrhage, and 9.6 % in those with traumatic brain injury. The etiology was due to SIADH (62 %; though 16.6 % were drug associated), hypovolemia (27 %), cerebral salt-wasting syndrome (CSWS) (4.8 %), fluid administration (3.7 %), and mixed SIADH/CSWS (2.7 %). Those who were hyponatremic had a longer hospital stay compared to normonatremic patients (19 days vs. 12 days, respectively). Severe hyponatremia was infrequent in this group; only 0.6 % of all the patients had a plasma sodium <120 mmol/L.

Pituitary surgery can be complicated by diabetes insipidus (DI) leading to polyuria, hyponatremia, or a combination of these two. Hensen et al. [33] reported on a series of 1,571 patients after transsphenoidal surgery for pituitary adenomas. Hyponatremia (serum sodium ≤132 mmol/L) was present in only 2.7 % of the patients on postoperative day 1 with subsequently more patients on day 7 (5 % of total); however, 40 % of the hyponatremic patients in the latter group were given desmopressin after surgery for treatment of polyuria. Overall, 8.4 % of the patients developed hyponatremia at some point up to the 10th postoperative day. Of these, a quarter developed symptomatic hyponatremia, but it was generally mild (nausea, headache, lightheadedness, vomiting) and transient. The etiology of hyponatremia was not elucidated, but the authors speculated that hyponatremia immediately after surgery was due to an acute release of arginine vasopressin (AVP) from pain or other non-osmotic stimuli whereas the delayed hyponatremia resulted from AVP release from an injured posterior pituitary gland (though some of the latter cases may have been drug induced). Kristof et al. [34] prospectively studied 57 successive patients undergoing transsphenoidal adenomectomy. Nine patients (16 %) had diabetes insipidus followed by hyponatremia (serum sodium <135 mmol/L), and

two of these patients had a second episode of DI. Isolated hyponatremia was present in 12 (21 %) of the patients with half developing mild clinical symptoms including headache, fatigue, nausea, and, in some, revulsion to drinking fluids. The patients had nadir median serum sodium of 132 mmol/L on day 9. SIADH was thought to be the cause of the hyponatremia as the ADH levels were not suppressed in these patients. One of the distinguishing parameters between SIADH and CSWS is that fluid restriction can result in volume depletion in those with CSWS due to continued natriuresis. In this study, one patient developed renal failure during fluid restriction possibly due to CSWS, though this possibility was not explored. SIADH seems to play a role in the pathogenesis of hyponatremia in this population, but the incidence of CSWS remains uncertain.

Hyponatremia with subarachnoid hemorrhage (SAH) due to a ruptured aneurysm is well documented. These patients are susceptible to cerebral vasospasm with subsequent cerebral infarction. Hyponatremia is important in these patients as it may be due to CSWS which can lead to volume depletion and potentiate vasospasm and cerebral infarction. Sayama et al. [35] performed a retrospective study in 169 patients evaluating the site of the hemorrhage and the incidence of hyponatremia. Overall, one-third of the patients developed hyponatremia (serum sodium $<$135 mEq/L). Interestingly, half of the patients with a rupture in the anterior communicating artery developed hyponatremia compared to about 20 % in the other sites. The authors suggested this disparity may be due to the fact that the posterior hypothalamus is perfused by branches from the anterior communicating artery, and vasospasm of these arteries can lead to hypothalamic dysfunction. Hasan et al. [36] evaluated 208 consecutive patients and found that 34 % of the patients developed hyponatremia (serum sodium $<$135 mmol/L) after SAH with a higher frequency of cerebral infarction noted in the hyponatremic group compared to the normonatremic group (24 % vs. 12 %, respectively).

Hyponatremia is also associated with traumatic brain injury (TBI) and can lead to neurological dysfunction and possible long-term sequela. In prospective studies, hyponatremia (plasma sodium $<$130 mEq/L) occurs in 20–30 % of patients [37, 38]. Half of the hyponatremic patients had at least one measurement below 125 mEq/L, and the average time to first detection of hyponatremia was 6 days [37]. Hyponatremia may occur in a variety of types of head injury including cerebral contusion, acute and chronic subdural hematomas, acute epidural hematoma, and diffuse axonal injury [39], but others [38] found that intraparenchymal lesions were the most common type (89 %).

The etiologies for hyponatremia differ among TBI patients with reports of SIADH, CSWS, and hypopituitarism. In the above studies, the authors [37, 39] were able to correct the sodium of most, though not all, of their patients with saline. Moro et al. [39] noted that 74 % of the hyponatremic patients corrected with saline infusions, but the rest required prolonged saline due to massive natriuresis. These patients were given hydrocortisone that reduced the sodium excretion and corrected the hyponatremia. Because of insufficient data, these authors were not able to elucidate the exact cause of the hyponatremia, though the pattern in some suggests CSWS. Whether SIADH or hypothalamic dysfunction leading to dysregulation of

Table 1.4 Studies of heart failure patients with hyponatremia

Heart Failure				
Study	Sodium	Frequency (%)	Sample Size	Study Type
OPTIMIZE-HF [42]	<135	20	48,612	R
OPTIME-CHF [43]	132–135	27	949	R/P
ESCAPE [44]	≤134	24	433	RCT
ACTIV in CHF [45]	<136	21	319	RCT

R retrospective study, *R/P* retrospective analysis of a prospective study, *RCT* randomized control trial

ADH secretion is at play is unclear, but other factors such as brain natriuretic peptide have been suggested to play a part in the desalination process. This still requires further investigation to elucidate the actual incidence of SIADH, CSWS, and hypopituitarism in TBI.

Adverse outcomes and long-term sequela are of concern in patients with intracranial insults. The presence of hyponatremia has been associated with a worse outcome [39], though others [38] have not seen such an association.

Heart Failure

Now classic studies from the 1980s highlighted the importance of hyponatremia in patients with congestive heart failure (CHF) [40]. It was noted that the presence of hyponatremia predicted increased mortality. Further, if treatment of heart failure resulted in a normalization of hyponatremia, mortality was improved [41]. More recent studies have further defined the incidence and significance of hyponatremia in heart failure.

Hyponatremia is seen in one-fifth to one-third of heart failure patients as reported in several large studies (see Table 1.4). In the OPTIMIZE-HF [42] study, about half of the patients had left ventricular systolic dysfunction, and the hyponatremic patients had a lower admission systolic blood pressure and atrial arrhythmias. In the OPTIME-CHF [43] study, the hyponatremic group had more severe heart failure with higher blood urea nitrogen (BUN) and a lower systolic blood pressure. In the ESCAPE Trial [44], a randomized control study of patients with a New York Heart Association class IV due to systolic dysfunction, 69 % of the hyponatremic patients had persistent hyponatremia at discharge. The group with persistent hyponatremia had lower baseline systolic blood pressure, higher serum urea nitrogen (SUN), and was more likely to be treated with spironolactone at baseline and receive larger doses of diuretics during their hospitalization.

Mortality is already high in heart failure patients, and the in-hospital mortality (~6 %) for the hyponatremic group is two to six times higher compared to the normonatremic group [42, 43]. The 60-day mortality was also higher in the hyponatremic patients (16 % vs. 6.4 %) [43]. As expected, those who corrected

their hyponatremia (serum sodium >135 mEq/L) at discharge had a lower 60-day mortality of 11 % compared to those that remained hyponatremic at discharge (17 %). Similarly, in the ESCAPE Trial, those with persistent hyponatremia had a twofold increase in 6-month all-cause mortality (31 % vs. 16 %). These studies are consistent with the thesis that correction of hyponatremia associated with improved heart failure confers a mortality benefit. Unfortunately, the improvement of the hyponatremia per se does not improve outcome [45] as the ACTIV in CHF trial demonstrated no significant difference in 60-day mortality or worsening heart failure between the vasopressin V2 Receptor antagonist groups and the placebo group.

Cirrhosis

Many cirrhotic patients have hyponatremia as demonstrated by a large population study performed by Angeli et al. [46]. They prospectively collected data on 997 cirrhotic patients in Europe, North and South America and Asia for 28 days in hospital and clinic settings in which inpatients accounted for about a half (53 %) of the study population. Mild hyponatremia (serum sodium of ≤135 mmol/L) was seen in 49 % of all the patients, and moderate hyponatremia (serum sodium of ≤130 mmol/L) was found in 28 % of inpatients (vs. 14 % of outpatients). Similar results were seen using these same levels of hyponatremia by Borroni et al. [47] (30 % of 156 consecutive cirrhotic patient admissions) and Porcel et al. [48] (35 % of 155 prospectively studied inpatients). In 126 consecutive ICU admissions, 29 % of critically ill cirrhotic patients had serum sodium of ≤130 mmol/L [49]. Angeli et al. [46] reported a frequency of 5.7 % for more severe hyponatremia (serum sodium ≤125 mmol/L), and only 1.2 % of the inpatient population had a serum sodium ≤120 mmol/L.

Various studies reveal that cirrhotic patients with hyponatremia have a higher frequency of hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, higher illness severity scores, sepsis, renal failure, and in-hospital mortality compared to normonatremic patients [46, 48, 49]. Borroni et al. [47] showed a death rate of 27 % in patients with a serum sodium ≤130 mmol/L (vs. 9 % in those that were normonatremic) and an even higher mortality of 48 % if the sodium was <125 mmol/L.

Infectious Diseases

Hyponatremia is common in infectious diseases such as HIV/AIDS, pneumonia, meningitis, and malaria. In a prospective study for a 3-month period [50] in patients with AIDS or AIDS-related complex, hyponatremia (serum sodium <135 mmol/L) was present in 38 % of their 167 hospitalized patients. The patients with

hyponatremia on admission were euvolemic (46 %) or hypovolemic (43 %) but most that developed hyponatremia after hospitalization were euvolemic (68 %) and had features consistent with SIADH. Pulmonary infections were the most common cause of SIADH with 93 % of the pulmonary infections due to *Pneumocystis carinii*. Cusano et al. [51] found similar results: one-third (31 %) had a serum sodium $\leq$130 mmol/L but in this study, most patients were hypovolemic (88 %). They noted that those with hyponatremia had a higher frequency of opportunistic infections, with 70 % having *Pneumocystis carinii* infection, almost three times higher than in the normonatremic group; cytomegalovirus infection was also more commonly found. A retrospective analysis of 71 hospitalized patients [52] found a serum sodium <133 mmol/L in half (52 %) of the patients, which was confirmed in a prospective portion of the study with 48 total patients. Again, *Pneumocystis carinii* pneumonia was found in 71 % of patients. Detailed studies in a subset of patients, including ADH levels, suggested SIADH in 15 of 16 patients. Dao et al. [53] reported a sodium <135 mmol/L in about half (46 %) of 661 consecutive women starting antiretroviral therapy in sub-Sahara, but it was not independently associated with mortality though other studies have reported about a twofold increase in mortality associated with hyponatremia compared to normonatremic patients [50, 51].

Community-acquired pneumonia (CAP) is associated with hyponatremia. A retrospective study found hyponatremia in 28 % of patients with CAP [54]. However, two prospective studies place the incidence closer to 10 % [54, 55]. Interestingly, hyponatremia (serum sodium <130 mmol/L) was more frequent in patients with legionella pneumonia at a rate of 29 % (vs. 6.5 % in those with CAP due to other organisms combined) [56].

Brouwer et al. [57] examined hyponatremia in community-acquired bacterial meningitis. A serum sodium <135 mmol/L was present in one-third (30 %) of admissions of 696 adults in this prospective study, but only 6 % had a serum sodium <130 mmol/L. The frequency of hyponatremia varied with a given organism; 33 % in pneumococcal meningitis, 21 % in meningococcal meningitis but unexpectedly high (73 %) in *Listeria monocytogenes* meningitis. In most cases (79 %), the hyponatremia resolved within 3 days, and it was not associated with adverse outcomes or increase in symptoms or complications. The etiology was not determined in this study.

Hanson et al. [58] evaluated 171 consecutive patients in Bangladesh for hyponatremia in severe malaria. On admission, more than half (57 %) of the patients had a plasma sodium <135 mmol/L, and one-third (30 %) had a plasma sodium of <130 mmol/L. The overall mortality rate was 40 %, but the patients that survived actually had lower admission plasma sodium compared to the 69 patients that died. This paradoxical benefit can be explained by a better conscious level (exhibited by a higher Glasgow Coma Scale) in those that survived and therefore continued to take in fluids and subsequently developed hyponatremia. They also noted that hyponatremia improved after crystalloid infusion, suggesting that hypovolemia, not SIADH, was the etiology.

Cancer-Related Hyponatremia

Doshi et al. [59] reported on a large retrospective study including 3,357 patients with cancer admitted to University of Texas M.D. Anderson Cancer Center and noted a serum sodium <135 mEq/L in about half (47 %) of the hospitalized patients (half on admission and a half after hospitalization). The hyponatremia was mild (serum sodium 130–134 mEq/L) in 36 %, moderate (serum sodium 120–129 mEq/L) in 10 %, and severe (serum sodium <120 mEq/L) in 1 % of the patients. Hematologic malignancies tended to have mild hyponatremia whereas patients with head-and-neck and gastrointestinal malignancies had more moderate to severe hyponatremia. Similar findings were reported in smaller retrospective studies [11, 60] but in a prospective study, Berghmans et al. [61] showed the incidence of hyponatremia (serum sodium ≤130 mEq/L) in a cancer hospital setting to be 3.7 %. Hyponatremia was found in all types of cancers with about one-third of the cases attributed to SIADH, another third to volume depletion, and the rest due to a variety of causes.

SIADH is a known cause of hyponatremia in cancer and has been more frequently observed in patients with lung cancers, occurring in about 10–15 % of the cases [62, 63]. Recently, several authors have speculated that atrial natriuretic peptide (ANP) could contribute to the development of hyponatremia in those with lung malignancy, but this was not confirmed by Johnson et al. [64] who investigated this question in a prospective study of 146 patients (22 % of whom had hyponatremia) with small cell lung cancer and nonsmall cell lung cancer.

Patients with malignancy have a high mortality rate, and hyponatremia has been associated as a possible risk factor. Two studies [59, 61] found that patients with hyponatremia had a threefold higher mortality rate and the hazard ratio for 90-day mortality worsens with more severe hyponatremia [59]. Hansen et al. [60] reported a median survival of 7.1 months for the hyponatremic patients compared to 11.2 months for those with normal sodium.

SIADH

SIADH is a common cause of hyponatremia, but the exact prevalence of SIADH is unclear as it is seen in a variety of clinical scenarios, illnesses, and associated with different medications. The diagnosis of SIADH can also be challenging due to the prerequisites needed to make the diagnosis. Volume status is difficult to measure and many times there is more than one possible cause of hyponatremia. Further, SIADH also has a similar biochemical and clinical profile to CSWS. SIADH is common in a variety of pathologies (like lung and CNS) and in hospitalized patients with a range from 2 % to 50 % of hyponatremic cases [23, 27, 38, 61, 65, 66] . It has also been reported with a number of drugs such as SSRI's and MDMA (3, 4-Methylenedioxymethamphetamine) [31, 67]. Anpalahan [24]

reported a rate of 25 % hyponatremic cases with half (51 %) of those cases attributed to SIADH. Nine cases had no apparent cause for SIADH and were presumed to be idiopathic SIADH. Of these, eight were older than 80 years old. The rest of the SIADH cases were thought to be due to some CNS or malignant cause or drug induced.

Cerebral salt wasting or renal salt wasting shares some features with SIADH. As mentioned, CSWS may be seen with CNS disease especially trauma or surgery. However, the true incidence of this entity has been a matter of debate and is discussed further in Chap. 4.

Psychiatric Diseases/Psychogenic Polydipsia

Hyponatremia in patients with psychosis is often multifactorial and is discussed in Chap. 9. Many of these patients have excessive water intake (psychogenic polydipsia) but given the large capacity of the normal kidney to excrete free water, polydipsia alone is not generally the only factor present. Psychogenic polydipsia itself is poorly understood, and the exact incidence is unknown. Some have suggested that polydipsia may be higher than 20 % in chronic psychiatric inpatients with 1–5 % developing symptoms of water intoxication [65]. A cross-sectional survey on 353 psychiatric inpatients [68] found a prevalence of polydipsia of 13 % in the chronic psychiatric inpatient population and 2.4 % of those patients had well-documented episodes of water intoxication. Forty-two percent of the polydipsic patients carried a diagnosis of schizophrenia. The sodium levels at the time of water intoxication ranged from 106 to 114 mmol/L with symptoms of vomiting, confusion, convulsion, and hypotonic coma. Notably, a third of these patients were considered at risk for water intoxication as they had a previous recorded episode of hyponatremia (sodium level $<$135 mmol/L).

Jose and Perez-Cruet [69] surveyed 239 patients in long-term psychiatric ward and noted that 16 (6.6 %) patients had a consistent history of compulsive water drinking (polydipsia) with half of these patients showing symptoms of water intoxication, mainly seizures. The serum sodium ranged between 110 and 131 mEq/L with most of the patients having a diagnosis of schizophrenia. Hariprasad et al. [70] evaluated 20 chronic polydipsic patients with hyponatremia in a psychiatric ward and found results consistent with reset osmostat. (As discussed in Chap. 2, some consider reset osmostat a subtype of SIADH but as discussed in Chap. 4, some consider this a separate entity.)

These studies show that hyponatremia is not rare in chronic psychiatric inpatients and is associated with excessive water intake but in the presence of SIADH and/or reset osmostat. Though antipsychotic medications can cause SIADH and hyponatremia, polydipsia has been curtailed in these schizophrenic patients with medical treatment of the schizophrenia [70].

Endocrine

Endocrine abnormalities are an infrequent cause of hyponatremia. A large retrospective study [71] examined the laboratory records of 15,080 patients in a large hospital and noted that 5.2 % of patients had a serum sodium <135 mmol/L. Hypothyroidism was found more frequently in the hyponatremic group compared to the normonatremic group (4.7 % vs. 1.7 %, respectively). This is similar to what others have shown in the HIV population [52]. Thus, although hypothyroidism is found in hyponatremic patients, a causal relationship is not shown in these studies.

Adrenal insufficiency is also seen within hyponatremic patients, but there a few studies that report on hyponatremia and adrenal insufficiency per se [50, 51]. The finding may be incidental and not clinically evident in some cases [52]. In patients with AIDS or AIDS-related hyponatremia attributed to adrenal insufficiency accounted for less than 5 % of the cases [72].

Exercise-Associated Hyponatremia

Exercise-associated hyponatremia (EAH) is seen in endurance events. Several studies have looked at the prevalence and risk factors leading to EAH. In a study of 488 runners in the 2002 Boston marathon [30], 13 % of the runners had a serum sodium <135 mmol/L with 0.6 % having critical hyponatremia (serum sodium <120 mmol/L). They noted that the hyponatremic group was more likely to have post-race weight higher than the prerace weight in 71 % compared to the normonatremic runners (29 %). Multivariate analysis showed an association of hyponatremia with weight gain, racing time >4 h, and body mass index extremes (which may explain the association with women). Chorley et al. [73] evaluated 96 Houston marathon runners and found an incidence of 22 % of runners with EAH (serum sodium <135 mmol/L). All of the hyponatremic runners were asymptomatic. They also noted that the lower post-race sodium was related to less weight loss during the race and a higher consumption of fluids during the race. Women had a positive fluid balance and less weight loss compared to their male counterparts even though they consumed fluids at a lower rate. In 2003, Reid et al. [74] evaluated 155 runners in a New Zealand marathon and found no incidence of hyponatremia. They noted that the climate was milder, there were fewer aid stations (every 5 km compared to every 1.6 km in many US races), and aggressive hydration was not emphasized.

From these and other studies, a consensus has been reached that certain risk factors could lead to hyponatremia. These include low body weight, female sex, >4 h exercise duration, slow running, race inexperience, excessive drinking behavior and high availability of drinking fluids, altered renal water excretory capacity, and extreme hot or cold environment [75]. This is discussed in more detail in Chap. 10.

Beer Potomania

Beer potomania is a rare cause of hyponatremia mainly due to a low solute intake and binge drinking. Hyponatremia is common in alcoholics and is seen in 5–13 % of these patients admitted to the hospital [76, 77]. Liver failure is a common cause. A prospective study [77] found that of the 127 patients with adequate information to analyze, only two of the 16 hyponatremic patients had beer potomania.

A literature review by Sanghvi et al. [76] summarized 22 patients with mild neurological symptoms (typically confusion) on presentation with mean serum sodium of 108 mEq/L due to beer potomania. They reported a high rate of severe complications (36 %) due to overcorrection with half developing osmotic demyelination syndrome and the other half died. Some of these patients had an overcorrection due to solute administration in the form of either empiric antibiotic administration or saline infusion and subsequent polyuria. Interestingly, because of volume depletion, some of the patients did not have the expected low urine osmolality on admission which made accurate diagnosis challenging.

Beer potomania is rare in this population but it is, nevertheless, seen and subject to a high degree of adverse outcomes. The physician should have a high index of suspicion in this chronic alcoholic population as it is at risk for complications.

Medications and Drugs

A great variety of drugs have been implicated with the development of hyponatremia. Within this section, we examine a handful of drugs with a more extensive discussion given in Chap. 6. Diuretics are known to cause hyponatremia, accounting for 15–50 % of the hyponatremic cases. In the study of 1,000 consecutive geriatric admissions [25] cited above, hyponatremia is present in 7 % of the patients with half of the hyponatremic patients receiving diuretics. The serum sodium was lower in the diuretic group compared to the non-diuretic group with individuals taking potassium-sparing diuretics having lower sodium than the others. In a prospective study [66] of 158 hyponatremic patients admitted to an internal medicine ward, 40 (25 %) patients had diuretic-induced hyponatremia. These 40 patients had lower mean sodium than the remaining hyponatremic patients (121.2 ± 7.2 vs. 126.4 ± 4.1 mEq/L). All of these patients were on a thiazide diuretic, which is expected, as thiazides inhibit water excretion but not urinary concentrating ability, and they were older than the other hyponatremic groups. Other studies have similarly reported about one-third of hyponatremia cases are associated with diuretic use [21, 22, 27] which is higher than diuretic use in the controls of about 15 % [21, 27]. These studies show that diuretic-induced hyponatremia is common in the hospitalized/elderly population, especially those treated with thiazide diuretics.

SSRI's are implicated in causing hyponatremia, though the reported frequency varies greatly. Wilkinson et al. [78] reported a retrospective and case control trial in

patients aged 65 and older in an inpatient/outpatient and rehabilitation setting and found hyponatremia (plasma sodium <130 mmol/L) after a median of 13.5 days with an incidence of about 0.5 %. Most (79 %) of the cases occurred within 3 weeks and in all cases within 10 weeks. The majority of cases (71 %) were women compared with controls, but these results were confounded by body weight as the hyponatremic cases tended to have lower body weights. In a prospective, longitudinal analysis [67], hyponatremia (plasma sodium <135 mEq/L) developed in 12 % of the patients aged 63–90 years old after initiation of paroxetine treatment. The mean time to development was 9 days. Most hyponatremic patients experienced mild symptoms including nausea and fatigue and only one patient complained of confusion. They also measured ADH levels and noted that the ADH levels were, inappropriately, not suppressed in the hyponatremic group.

Desmopressin has long been used for the treatment of nocturia. Pooled data from three multicenter phase III trials [79] noted mild hyponatremia (serum sodium 130–134 mmol/L) in 15 % of the patients and moderate hyponatremia (serum sodium <130 mmol/L) in 4.9 % of patients. These hyponatremic patients were older than 65 years old, had lower serum sodium at baseline, higher basal 24-h urine volume per body weight, and had gained weight at the time of the serum sodium nadir. A double-blind study [80] found similar results with 3 % of the population developing moderate hyponatremia (serum sodium <130 mmol/L); most were above age 65. The most serious symptom was headache but most patients were asymptomatic. Hyponatremia has also been reported in children treated with desmopressin. Postmarketing safety data revealed 151 cases of hyponatremia in children where most (145) of the children received intranasal desmopressin and the rest had an oral formulation. Symptoms including headache, nausea, and vomiting were seen in these children [81].

Conclusions

Hyponatremia is a common electrolyte abnormality that is seen in various settings and to varying degree. The impact of hyponatremia is larger with a lower sodium level as it may represent a sicker population or deregulation of the sodium/water homeostasis and make patients more susceptible to complications if it is not corrected or corrected too rapidly.

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