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Hyponatremia and Psychiatric Diseases

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Abstract

Eating disorders, psychotic illnesses, and substance use disorders are some of the more common psychiatric conditions encountered in clinical practice that are associated with hyponatremia. The mechanisms that lead to hyponatremia vary, and at times hyponatremia may be a result of a drug side effect or drug-drug interaction. Additionally, hyponatremia from a non-psychiatric condition may lead to psychiatric symptomatology. Given the potential for hyponatremia to cause significant morbidity and potential mortality, clinicians are urged to consider screening for plasma sodium in patients at risk of hyponatremia, such as patients in the three categories of psychiatric conditions described above. Treatment of hyponatremia consists of various acute interventions, with consideration that treatment of the underlying psychiatric condition may help to diminish or eliminate the frequency of hyponatremic episodes in the long run.

Keywords: hyponatremia, anorexia nervosa, bulimia nervosa, psychosis, alcohol use disorder

1. Introduction

Sodium abnormalities can be seen in various psychiatric diseases. Common conditions include eating disorders, psychotic illnesses, and certain substance use disorders. Additionally, hyponatremia of any cause, including from drug side effects in patients being treated for psychiatric illnesses, can cause or worsen psychiatric conditions and may lead to medical comorbidities. References used in this chapter include articles from an online PubMed search of hyponatremia and psychosis spanning the past 50 years, and various Up-to-date review articles. In this chapter we dissect these conditions and open with a typical patient case.

1.1 Case

Lucia is a 19 year old junior majoring in Mathematics and Literature. She runs cross-country and has fainted multiple times while training with her teammates. On the recommendation of her coach she went to the student medical center for a wellness check. She looks thin and athletic. Vital sign checks show postural hypotension and orthostatic increase in pulse rate. Her BMI is calculated at 18 kg/m². She reports
otherwise good health and no psychiatric concerns. She is doing well in school and excelling on the cross-country team.

1. What additional questions might you ask to elucidate the cause of her syncopal episodes? 2. What additional investigation would you find helpful?

2. Eating disorders and hyponatremia

2.1 Three main types of eating disorders

Eating disorders are characterized by a disturbance in eating or eating related behavior and body image associated with substantial distress and psychosocial impairment and/or jeopardizing physical health [1]. Anorexia Nervosa, Bulimia Nervosa, and Binge Eating Disorder are the most well-known and best understood eating disorders. Other recognized eating disorders include avoidant/restrictive food intake disorder, pica, and rumination disorder. This classification scheme is mutually exclusive, such that during one-episode patients can carry only one diagnosis at a time. In this chapter we discuss the diagnostic categories that lead to hyponatremia and then focus on detecting and treating hyponatremia in the eating disordered patient [2].

Anorexia Nervosa is distinguished by severe restriction in nutritional intake leading to a BMI that is less than 18.5 kg/m$^2$ in adults, an intense fear of becoming fat, gaining weight, and distortion in body shape and image. This is accompanied by behaviors that continue to interfere with weight gain and that stimulate weight loss. These behaviors include exercising, restricting food, eating low calorie foods, or purging by using laxatives or diuretics to lose weight.

As defined by DSM-5 [1], anorexia nervosa—restricting subtype describes an individual whose weight loss has been accomplished primarily by dieting and fasting and has not engaged in recurrent episodes of binge eating or purging in the last 3 months. In Anorexia nervosa—binge-eating/purging subtype, the individual meets criteria for anorexia nervosa and has engaged in episodes of binge-eating and purging over the last 3 months.

Bulimia Nervosa is characterized by recurrent episodes of binge eating and compensatory behavior aimed at preventing weight gain, occurring at least once a week for at least 3 months. Like in the binge-purge subtype of Anorexia Nervosa, these purging behaviors may include self-induced vomiting, misuse of diuretics, or laxatives, or excessive exercise. Patients may also restrict by fasting.

2.2 Electrolyte disturbances

If untreated and persistent, these two types of eating disorders result in electrolyte and acid-base disturbances, affecting serum and urine sodium, potassium, and chloride, and serum bicarbonate and pH [3]. Common electrolyte disturbances include hypokalemia and hyponatremia [4]. Hyponatremia is defined by a serum sodium concentration of <135 mEQ/L. Patients who purge consistently lose sodium through fluid output; self-induce vomiting, laxatives abuse leading to diarrhea; and diuretic abuse, leading to excessive urination. This decrease in effective circulating vascular volume stimulates the release of antidiuretic hormone (ADH) from the pituitary gland leading to water reabsorption through the kidneys. The body’s attempt to preserve volume leads to dilution of the sodium already present in circulation. Hyponatremia in our eating disordered patients can be associated with low, normal or high serum tonicity. Hyponatremia associated with hypovolemia is as a result of low serum tonicinity. Hyponatremia may also result from excessive water intake or impaired renal sodium reabsorption due to chronic starvation.
2.3 Identifying hyponatremia

A quick screen can be utilized to investigate eating disordered patterns. Clinicians should use a validated eating disorder questionnaire, like the Eating Disorder Questionnaire Online (EDQ-O) or the SCOFF (Sick Control, One, Fat, Food) questionnaire to assess for the presence of an eating disorder [5]. On physical examination, patients who purge consistently or who restrict may appear volume depleted with orthostatic decreases in blood pressure, increases in pulse rate and decreased skin turgor. In addition to a basic metabolic panel, urine electrolyte screens should be completed to help elucidate the etiology of the hyponatremia. Patients who misuse prescribed diuretics or who use copious amounts of over the counter diuretics will not have low urine sodium. On the other hand, patients who self-induce vomiting or diarrhea will have low urinary sodium because of increased sodium retention through the kidneys.

2.4 Treatment

Treatment depends on the severity of hyponatremia. In the case of patients with eating disorders, psychiatrists and nutritionists should be consulted and involved in treatment and care to facilitate discontinuation of purging, and excessive water drinking [6]. Some hospitals have developed protocols for treating such patients, including observed meals and caloric counting to ensure a smooth recovery when food is re-introduced and for prevention of refeeding syndrome [7].

3. Psychotic illnesses, bipolar illnesses, and obsessive-compulsive disorder (OCD) affecting serum sodium

3.1 Psychotic illnesses

One of the most common psychotic illnesses that affect serum sodium is schizophrenia. As defined by DSM-5 [1], schizophrenia is characterized by two or more of the following symptoms including delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms (i.e. diminished emotional expression) that are present for a significant portion of a 1-month period and continuous signs of disturbance in functioning level present for at least 6 months. Patients with schizophrenia can experience primary psychogenic polydipsia (PPD), characterized by an increase of fluid intake along with excretion of excessive amounts of dilute urine exceeding 40–50 mL/kg of body weight [8]. It is hypothesized that this occurs in patients with schizophrenia due to elevated levels of dopamine that stimulate the thirst center [8]. In patients with schizophrenia, polydipsia prevalence is estimated at 6–20%, and complications can include not just hyponatremia but rhabdomyolysis as well [9]. Severe water intoxication has also been reported in a patient with delusional skin infestation leading to hyponatremia [10].

3.2 Bipolar illness

PPD has also been implicated in psychiatric patients with bipolar I disorder in a manic state whose increase in fluid intake can lead to hyponatremia [8]. As defined by DSM 5, a manic episode is a distinct period of abnormally and persistently elevated, expansive or irritable mood with increased activity or energy lasting at least 1 week that is not attributable to physiological effects of substances with three or more of the following symptoms present including inflated self-esteem,
decreased need for sleep, pressured speech, flight of ideas, distractibility, increased goal directed activity, and excessive involvement in activities that have a high potential for painful consequences such as gambling, sexual indiscretions, and unrestrained buying sprees. The presence of mania distinguishes bipolar I from bipolar II; in bipolar I a patient must meet criteria for a manic episode, which may have been preceded or followed by a hypomanic or major depressive episode. Additionally, as defined by DMS 5 [1], bipolar disorder type II is diagnosed when the individual meets criteria for a current or past hypomanic episode and a current or past major depressive episode. A hypomanic episode is defined by DSM 5 [1] as a distinct period of abnormally and persistently elevated, expansive or irritable mood with increased activity or energy lasting at least 4 days with three or more of the following symptoms present including inflated self-esteem, decreased need for sleep, pressured speech, flight of ideas, distractibility, increased goal directed activity, and excessive involvement in activities that have a high potential for painful consequences such as gambling, sexual indiscretions, and unrestrained buying sprees. Major depressive episode includes 5 or more of the following symptoms over a 2-week period that represent a change from previous functioning such as depressed mood, diminished interest in activities, significant change in weight, insomnia or hypersomnia, psychomotor agitation or retardation, loss of energy, feelings of worthlessness, decreased ability to concentrate, and recurrent thoughts of death.

3.3 Obsessive compulsive disorder (OCD)

Obsessive-compulsive disorder as defined by DSM 5 [1] is characterized by the presence of obsessions, compulsions or both. Obsessions are recurrent or persistent intrusive thoughts that cause marked anxiety or distress that individuals try to ignore or suppress by performing compulsions such as repetitive behaviors or mental acts including hand washing, praying, or checking behaviors. The obsessions and compulsions are time consuming, and distressing, and are not attributed to another medical condition. An interesting case of an Indian woman has been reported in the literature, where her behaviors of excessive water intake, intrusiveness, excessive washing, cleaning, checking and perfectionism led to a diagnosis of OCD. She had experienced recurrent seizures with no benefit from antiepileptic medication, and only after further assessment it was discovered that her urge to drink excessive water led to consumption of 7 L of water producing hyponatremia and seizure [11]. This case is important because it highlights how a psychiatric condition (OCD) can present as a neurological emergency [11].

4. Low serum sodium from other medical conditions contributing to mental health conditions

Exclusive relationships between hyponatremia, depression symptoms, and cognitive impairments have been reported in patients with chronic kidney disease who are also undergoing hemodialysis [12]. In DSM-5 [1], major depressive disorder is defined as a change from previous functioning that includes 5 or more of the following symptoms over a 2-week period of time such as depressed mood, diminished interest in activities, significant change in weight, insomnia or hypersomnia, psychomotor agitation or retardation, loss of energy, feelings of worthlessness, decreased ability to concentrate, and recurrent thoughts of death. Major neurocognitive disorder is characterized by significant cognitive decline from a previous level of functioning in one or more cognitive domains including complex attention,
executive function, learning and memory, language, perceptual motor, or social cognition that interfere with independence in everyday activities.

Hyponatremia has also been reported in association with catatonia and delirium, highlighting the profound effect that hyponatremia can have on one's mental status [13]. As defined by DSM 5 [1], catatonia includes a clinical picture dominated by three or more of the following symptoms including stupor, catalepsy (passive induction of posture held against gravity), waxy flexibility (slight, even positioning by examiner), mutism, negativism (opposition or no response), posturing, mannerism (odd, circumstantial caricature of normal actions), stereotypy (repetitive, abnormally frequent, non-global directed movements), grimacing, agitation, echolalia (mimicking another's speech), and echopraxia (mimicking another's movements). Mechanisms of hyponatremia leading to catatonia are not well elucidated. Based on case reports, it has been demonstrated multiple times that catatonia and delirium do occur in the context of hyponatremia. Some hypothesize that vasopressin regulation mediates the development of hyponatremia when one has catatonia with psychosis. While others argue that because only some Addison's disease patients develop hyponatremia (potential implication of aldosterone as regulator of sodium and water balance in the distal tubules and collecting ducts of the kidneys) and only some of those develop catatonia that therefore there is a presence of susceptibility of unknown reasons with hyponatremia causing catatonia [13]. DSM 5 [1] defines delirium as a disturbance in attention, awareness, and cognition that develops over a short period of time and tends to fluctuate in severity over the course of the day.

5. Drug side effects and drug-drug interactions affecting serum sodium in patients being treated for psychiatric conditions

5.1 Antidepressants and non-steroidal anti-inflammatory drugs (NSAIDs) implicated in hyponatremia

Among the classes of medications used to treat psychiatric conditions there are many side effects and interactions that may alter serum sodium. This is a critical consideration as many of the symptoms of hyponatremia, particularly generalized malaise and alterations in appetite can mimic symptoms of depression. A recent case report documented duloxetine induced hyponatremia, including symptoms such as “unsteady gait, dizziness, nausea, general malaise and poor appetite,” resolved by discontinuing duloxetine [14]. Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), such as duloxetine, have been associated with syndrome of inappropriate antidiuretic hormone (SIADH) with resulting hyponatremia. Hyponatremia results from an inappropriately high release of antidiuretic hormone (ADH) from the posterior pituitary, which results in an excess retention of water and a low serum osmolality. In particular SNRIs act primarily to inhibit the reuptake of both serotonin and noradrenaline, and in experimental models it has been shown that both serotonin and noradrenaline can result in the increased release of ADH (in rat models serotonin (5-HT) activated 5-HT1A receptors cause sympathoexcitation of SHT1C and SHT2 receptors and the release of ADH; also stimulation of the paraventricular and supraoptic nuclei with norepinephrine can increase release of ADH within the serum) [14]. Therefore, through these mechanisms it is hypothesized that SNRIs cause SIADH in patients, a life-threatening side effect that must be monitored for by clinicians.

A case report of a patient diagnosed with schizophrenia, taking desmopressin and meloxicam identified that NSAIDs can significantly augment hyponatremia
by “increas[ing] water retention” [15]. Notably, the worsened water retention is particularly problematic for patients on desmopressin, and complete resolution of symptoms occurred after desmopressin was tapered and meloxicam stopped, with normalization in plasma sodium [15] (Figure 1, used with permission from authors).

5.2 Other medications and interactions implicated in hyponatremia

Fabrazzo et al. [16] discuss three cases involving delorazepam, olanzapine and fluvoxamine, respectively, in which patients with various presentations of bipolar disorder were hospitalized, and hyponatremia was discovered on admission. Workup revealed SIADH. Multiple interventions were trialed, including administration of hypertonic saline, and decreasing doses of various medications. It was not until the offending medications were removed that patients demonstrated resolution of their hyponatremia. Notably, olanzapine, fluvoxamine and delorazepam were being administered in conjunction with other medications that may have contributed to the hyponatremia. In the case of the patient taking delorazepam, they also were prescribed oxcarbazepine, which ultimately was replaced with gabapentin. In the case of the patient taking olanzapine, he also was taking delorazepam and oxcarbazepine. Likewise, the patient on fluvoxamine was also taking oxcarbazepine. These medications in conjunction with one another appear to have an additive property on hyponatremia.

5.3 Additional considerations for antipsychotics and hyponatremia

Antipsychotic medications alone have been reported in the literature to be associated with hyponatremia; however, recently, the long-acting risperidone injectable treatment has been implicated in hyponatremia as well. In this case, the patient did not improve simply with the removal of risperidone, due to the extended half-life, and ultimately required Tolvaptan administration [17]. The half-life of these medications may be an important factor in determining the management of subsequent hyponatremia. Along a similar vein, Fabrazzo et al. [16] detail that hyponatremia and other electrolyte derangements are often only detected in patients with psychiatric diagnoses when they are hospitalized. This is a critical consideration for clinicians in terms of practice, particularly whether there is an impetus for psychiatrists

Figure 1.
Plasma sodium levels over time.
to consider routinely monitoring electrolytes of patients on longstanding medications with the potential for these derangements, especially in patients with bipolar disorder.

5.4 Practice considerations

There currently are no routine guidelines for screening of electrolyte abnormalities among patients with psychiatric diagnoses and this should be further evaluated given the range of dangerous consequences of hyponatremia, including seizure, as demonstrated in at least one of the cases delineated above [15].

6. Alcohol and other substance use disorders affecting serum sodium

6.1 Alcohol and hyponatremia

Substance use is also implicated in derangements of serum sodium, particularly among patients who abuse alcohol and MDMA. As defined by DSM 5 [1], alcohol use disorder is a pattern of alcohol use within the past 12 months that has led to significant impairment in one’s life characterized by at least two of the following including alcohol taken in larger amounts, persistent desire to cut down, increased time obtaining alcohol, cravings, continued use despite recurrent impairment in social functioning, developed tolerance, and withdrawal symptoms present when alcohol use is ceased. As delineated in previous sections, there are profound potential consequences of hyponatremia, particularly because of sodium’s role in maintaining nerve impulse conduction and neuromuscular excitability. Michal et al. [18] observed that in patients with likely alcohol use disorder, the level of derangement in serum sodium was associated with the worsening of physical and psychological quality of life; that is to say, patients with severe hyponatremia (<120 mmol/L) were likely to have worse quality of life than patients with low hyponatremia (>135 mmol/L) [18]. The specific causal pathways are not delineated; however, beer potomania is an observed phenomenon in which dietary insufficiency of protein, coupled with dietary sodium results in a sort of dilutional hyponatremia. It is possible that patients with more severe hyponatremia may be further in their disease course, ultimately consuming more alcohol.

6.2 MDMA (3,4-methylenedioxymethamphetamine) and hyponatremia

Stimulant use disorder in DSM-5 [1] is defined as a pattern of stimulant use within the past 12 months that has led to significant impairment in one’s life characterized by at least two of the following including the stimulant is taken in larger amounts, persistent desire to cut down, increased time obtaining the stimulant, cravings, continued use despite recurrent impairment in social functioning, developed tolerance, and withdrawal symptoms present when stimulant use is ceased. MDMA (3,4-methylenedioxymethamphetamine), a stimulant, is thought to be associated with hyponatremia because of increased diaphoresis, yielding sodium loss, and compensatory water intoxication. It is not a common side effect of MDMA use; however, Armitage et al. [19] presented a case report of an 18-year-old woman who had a generalized tonic-clonic seizure in the setting of hyponatremia from MDMA intoxication. This woman’s serum sodium was 121, notably close to what many would argue is severe hyponatremia. Notably, MDMA related hyponatremia with seizure is more common among young women under 30 years of age, particularly because of estrogen inhibiting the Na+/K+-ATPase. This ultimately inhibits
a known compensatory mechanism for cerebral edema, which may place young women at increased risk of neurological impacts of hyponatremia with MDMA use. Further, a metabolite of MDMA, 4-hydroxy-3-methoxymethamphetamine (HMMA), is documented to stimulate ADH release, which can worsen hyponatremia. These are vital considerations given the potential sequela of seizure, and the urgency of its management.

7. General treatment considerations for hyponatremia in psychiatric illnesses

Here, we aim to describe general considerations of hyponatremia by going over symptoms, treatment, and cautions.

7.1 Summary of general symptoms of hyponatremia

Symptoms of hyponatremia can be thought of as severe, moderate, and mild. Severe symptoms are red flag signs that include seizure and changes in cognition that can rapidly progress to coma and death. These symptoms are classically correlated with serum levels of less than 120. As such, these are the constellation of symptoms that would require hospitalization. Moderate and mild symptoms differ in severity but include flu like symptoms of headache, myopathy, and general malaise; these symptoms are observed mostly with sodium serum level ranges from 120 to 135. Lastly, there are patients who have low serum levels but are generally asymptomatic, with minimal changes in gait or sensorium [20].

7.2 Treatment of hyponatremia and cautions

When treating hyponatremia, it is important to recognize that there is a high risk of morbidity and mortality in conditions where hyponatremia develops within 48 h, post-op hyponatremia in female and pediatric populations, patients with history of cerebral pathology, as well as those presenting with psychosis (because they could have ingested large amounts of water). Regardless of symptom severity, it is important to note that increasing serum sodium level by 4–6 mEq/L in 24 h can reverse symptoms, and the rate should never exceed 8 mEq/L in a day, as rates faster than this can increase risk of demyelination [20]. Asymptomatic hyponatremia, if mild, may be left untreated.

Interventions commonly used in the context of treating hyponatremia include fluid restriction, increasing dietary salt, potassium replacements, hypertonic saline, and vasopressin antagonists, with selection based on the etiology and severity of the hyponatremia. Fluid restriction is most helpful in the context of volume overload (such as heart failure or cirrhosis), SIADH, renal failure, or if the patient has polydipsia. The amount of fluid restriction is determined often with nutritional consultation; this is the gold standard approach in treatment of SIADH. Patients may initially start with fluid restriction to 500 mL/d. Pharmacotherapy is typically considered if serum sodium has not improved with fluid restriction over 48 h [21].

Pharmacotherapy includes a broad range of options, including dietary salts and oral salt tablets, potassium replacements and vasopressin antagonists. Dietary salts and oral salt tablets are generally utilized for patients with mild to asymptomatic symptoms with SIADH. Potassium replacements are helpful when patients are developing conditions that are causing hypokalemic states as well, such as inappropriate diuretic uses and excessive vomiting. These may be associated with feeding and eating disorders, and additional considerations for the treatment of those
disorders may include 1:1 supervision for prevention of continued vomiting, and consultation with nutrition to minimize risk of refeeding during early hospitalization. Vasopressin antagonists will cause water loss, making it non-ideal for patients with volume deficits.

The clinician must always be wary of any contributing factors causing the hyponatremia; for example, if the patient has adrenal insufficiency, glucocorticoid replacement will be crucial. In this case, endocrinology consultation may be appropriate. Likewise, if the patient has drug induced SIADH, it is important to re-visit the necessity of the drugs and to find replacements if able; common culprits include SSRIs like fluoxetine and sertraline [20]. The clinician and the patient should have a conversation about the risks, benefits, and alternatives to continuing treatment with an offending agent and informed consent should be documented whether the medication is maintained or switched. In patients with psychogenic polydipsia associated with antipsychotic medication use, treatment of the underlying psychotic disorder coupled with behavioral intervention to limit water intake may decrease the frequency of hyponatremic episodes and lessen morbidity. In patients with substance use disorders, particularly alcohol use disorder, psychoeducation and motivational interviewing surrounding their substance use disorder and risks of hyponatremia, including increased risk of seizure, may be a helpful part of decreasing use of substance. These patients should also be offered medication assisted treatment for their substance use disorder when appropriate and desired by the patient.

In sum, hyponatremia in psychiatric conditions is best treated in a comprehensive, multi modal approach. With many etiologies, including SIADH, endocrine pathologies, feeding and eating disorders, and delirium, consultation with different medical specialties and nutritional teams may augment and improve the treatment of hyponatremia. Regardless of etiology, psychoeducation and involvement of the patient in shared decision making is essential in understanding the future course of treatment.

8. Conclusion

Hyponatremia is a complex electrolyte disturbance which can both manifest with psychiatric symptoms, and can be associated with psychiatric disease itself. Eating disorders, psychotic illnesses, and substance use disorders are some of the more common psychiatric conditions encountered in practice that are associated with hyponatremia. The mechanisms that lead to hyponatremia vary, and at times hyponatremia may be a result of a drug side effect or drug-drug interaction. Given the potential for hyponatremia to cause significant morbidity and potential mortality, clinicians are urged to consider screening for plasma sodium in patients at risk of hyponatremia, such as patients in the three categories of psychiatric conditions described above. Treatment considerations include: (1) understanding the underlying etiology of the hyponatremia, (2) asymptomatic mild hyponatremia may not need treatment, (3) fluid restriction is the initial treatment of choice for SIADH, (4) hypertonic saline is used to correct moderate-severe hyponatremia, but should be done only under the guidance of medical teams to avoid demyelination syndromes, (5) there may be other considerations, such as 1:1 supervision for feeding-eating disorders, (6) specialty consultation may be appropriate in determining course of treatment, such as nutrition for advancement of diet, or endocrinology for concomitant adrenal pathology. Treatment of hyponatremia consists of various acute interventions, with consideration that treatment of the underlying psychiatric condition may help to diminish or eliminate the frequency of hyponatremic episodes in the long run.
9. Case consideration

1. The patient should have a comprehensive assessment, which includes a medical interview, physical exam, and tests as needed. This assessment should include questions about diet, alcohol and drug use, exercise regimen, and past and current medical and psychiatric histories.

2. Additional investigations can include checking blood electrolytes and an EKG. In patients with eating disorders, one can see derangements in sodium and potassium (usually hyponatremia or hypokalemia or both). EKG may show QT prolongation.
References


