ORIGINAL RESEARCH PAPER

Clinical Research

SUMMARY ABOUT HYPONATREMIA AND PSYCHIATRIC DISORDERS

KEY WORDS:

Llerena Jurado María Ruth*	Independent investigators. *Corresponding Author
Peñafiel Erazo Adrián Rodrigo	Independent investigators.
Molina Pinto Janine Alejandra	Independent investigators.
Núñez Peñaloza Soraya Marianela	Independent investigators.
Mayorga Poveda Johanna Paulina	Independent investigators.
Martínez Naranjo Carol Michelle	Independent investigators.

ABSTRACT

Antidepressants are routinely used by General Practitioners (GP) as well as Psychiatrists to treat Depression. They are tolerated well. However, in certain patient populations, they are associated with SIADH (Syndrome of Inappropriate Anti-Diuretic Hormone Secretion) and Hyponatremia. Various research studies have shown that all antidepressants are associated with Hyponatremia. Hyponatremia as a side effect of antidepressant therapy is more commonly seen in old age, chronic Kidney disease and Hypothyroidism.
In this article, the authors discuss in relation to Hyponatremia and psychiatric disorders.

INTRODUCTION

Hyponatremia is one of the most common electrolyte disturbances in which patients present with psychiatric symptoms but often go unrecognized and undiagnosed.

Psychotropic drugs which can cause hyponatremia are antidepressants like serotonin reuptake inhibitors (SSRIs) (escitalopram, sertraline, fluoxetine, and paroxetine), antiepileptics such as carbamazepine and oxcarbazepine, and antipsychotics such as risperidone, clozapine, amisulpride, aripiprazole, and haloperidol.

Classification

Hyponatremia presents as hypertonic or hypotonic; however, only hypotonic hyponatremia is of clinical relevance. Hypotonic hyponatremia is categorized by severity and volume status. Severity of hyponatremia is classified as acute or chronic, differentiated by sodium levels and patient symptoms. Mild-to-moderate hyponatremia is a more chronic and asymptomatic condition and is defined as a sodium concentration of 120 to 135 mEq/L. Severe hyponatremia is a medical emergency and is usually defined as a sodium concentration of <120 mEq/L or hyponatremia with symptoms that may include seizures, coma, and respiratory arrest.

After severity is assessed, the patient's volume status is classified as hypervolemic (increased total body water), euvolemic (increased total body water but not clinically significant on physical examination), or hypovolemic (low total body water). This discussion will focus primarily on euvolemic hyponatremia induced by SIADH (syndrome of inappropriate antidiuretic hormone secretion) and psychogenic polydipsia.

Diagnosis and Assessment

The fundamental criteria considered when diagnosing hyponatremia are plasma osmolality, urinary electrolytes, volume status, fractional excretion of sodium (FeNa), and the ability to rule out hypothyroidism and glucocorticoid deficiency.

Hypovolemic hyponatremia is usually seen in patients presenting with severe diarrhea or vomiting and urine sodium values <30 mmol/L. In euvolemic patients, hyponatremia is most often due to SIADH, and patients typically have urine sodium levels >40 mEq/L. Patients presenting with SIADH are usually asymptomatic unless the sodium level is below 120 mEq/L. Free water excretion is impaired in SIADH, as evidenced by urine osmolality levels >100 mOsm/kg.

Main types of eating disorders with hyponatremia

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. 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.

Anorexia Nervosa is distinguished by severe restriction in nutritional intake leading to a BMI that is less than 18.5 kg/m2 in adults, an intense fear of becoming fat, gaining weight, and distortion in body shape and image.

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.

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.

Common electrolyte disturbances include hypokalemia and hyponatremia. 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 tonicity. Hyponatremia may also result from excessive water intake or impaired renal sodium reabsorption due to chronic starvation.

Psychotic Illnesses

One of the most common psychotic illnesses that affect serum sodium is schizophrenia. 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. It is hypothesized that this occurs in patients with schizophrenia due to elevated levels of dopamine that stimulate the thirst center.

Drugs

Psychotropic agents have often been implicated in the causation of hyponatremia, including both antidepressants (tricyclics, selective serotonin reuptake inhibitors [SSRIs], and monoamine oxidase inhibitors) and antipsychotic drugs (phenothiazines and butyrophenones).

Known risk factors for antidepressant-associated hyponatremia are advanced age, female sex, low body weight, low baseline serum sodium, and abnormal potassium level as well as other medical conditions such as heart failure, malignancy, liver disease, adrenal insufficiency, and possibly hypothyroidism.

Evidence suggests serotonin (5-hydroxytryptamine, 5-HT) and 5-HTergic drugs can induce enhancement of both central 5-HT transmission and antidiuretic hormone (ADH) secretion at the level of the posterior pituitary, resulting in SIADH-associated hyponatremia. Multiple 5-HT receptors (5-HT2, 5-HT4, and 5-HT7 receptors) engage in the regulatory pathway, with 5-HT2 receptors being the predominant group. Additionally, dopamine modulates the activity of ADH secretory cells responding to changes in osmolality and stimulates ADH release from the hypothalamus, predominantly via D2 receptors. Duloxetine not only inhibits the reuptake of 5-HT and norepinephrine but also increases dopamine, specifically in the prefrontal cortex. Duloxetine can affect multiple neuroendocrine pathways and thereby interfere with ADH secretion.

Dopamine (DA), released from the neurons of the substantia nigra pars compacta into the striatum, plays an important role in regulating normal and abnormal behaviors. Moreover, dysfunctions of dopaminergic neurotransmission are involved in the pathophysiology of various neuropsychiatric disorders including Parkinson's disease, schizophrenia, attention deficit hyperactivity disorder, drug abuse and depression.

Escitalopram, one of the newest additions to the Selective serotonin reuptake inhibitors (SSRIs), is a pure S-enantiomer of racemic citalopram and is the most selective among the SSRIs. Escitalopram is the mainstay pharmacotherapy for depressive disorders in the elderly due to their wider safety margin.

Escitalopram as the indicative drug for hyponatremia is reported much less compared to other SSRIs. The mechanism of action is hypothesized to be syndrome of inappropriate secretion of antidiuretic hormone.

Fluoxetine (an SSRI) is used for the treatment of depression, anxiety disorder, obsessive-compulsive disorder, and bulimia nervosa. Fluoxetine (an effective and well-tolerable antidepressant) has the favourable adverse effect profile. The most common side effect of it are nausea, headache, diarrhoea, and insomnia. Sedation and orthostatic hypotension are less common as side effects. But in the literature, hyponatremia due to fluoxetine use has not yet been reported in young patients without risk factors.

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.

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. Asymptomatic hyponatremia, if mild, may be left untreated.

CONCLUSION

Hyponatremia is a complex electrolyte disturbance which can both manifest with psychiatric symptoms.

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.

REFERENCES

1. Cleare A, Pariante CM, Young AH, Anderson IM, Christmas D, Cowen PJ et al; Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychop harmacology guidelines; Journal of Psychopharmacology 2015: 29:459–525.
2. Gandhi S, Shariff SZ, Al-Jaishi A, Reiss JP, Mamdani MM, Hackam DG, Lihua Li L, McArthur E, Weir MA, Garg AX: Second-Generation Antidepressants and Hyponatremia Risk: A Population-Based Cohort Study of Older Adults. Am J Kidney Dis. 2017;69(1):87-96
3. Leth-Møller KB, Hansen AH, Torstensson M, et al: Antidepressants and the risk of hyponatremia: a Danish register-based population study. BMJ Open 2016; 6:e011200. doi:10.1136/bmjopen-2016- 011200
4. Sivaraman S, Rajajeyakumar M. Psychiatric aspects of hyponatremia – A clinical approach. J Psychol Psychother 2016;6:1-2
5. Arieff AI, Llach F, Massry SG. Neurological manifestations and morbidity of hyponatremia: Correlation with brain water and electrolytes. Medicine (Baltimore) 1976;55:121-9
6. Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. Am J Kidney Dis 2008;52:144-53.
7. Ryan M, Adams AG, Larive LL. Hyponatremia and leukopenia associated with oxcarbazepine following carbamazepine therapy. Am J Health Syst Pharm 2001;58:1637-9.
8. Fabian TJ, Amico JA, Kroboth PD, Mulsant BH, Corey SE, Begley AE, et al. Paroxetine-induced hyponatremia in older adults: A 12-week prospective study. Arch Intern Med 2004;164:327-32
9. Bojdani E, Chen A, Buonocore S, Li K, Gurrera R. Meloxicam-desmopressin drug-drug interaction producing hyponatremia. Psychiatry Research. 2019; 279:284-286. DOI: 10.1016/j.psychres.2019.05.009. pii: S0165-1781(19) 30 250-1
10. Fabrazzo M, Fuschillo A, Perris F, Catapano F. The unmasking of hidden severe hyponatremia after long-term combination therapy in exacerbated bipolar

patients: A case series. International Clinical Psychopharmacology. 2019;34 (4):206-210. DOI: 10.1097/YIC.0000000000000265
11. Armitage MC, Bryant RJ, Page CB. Severe hyponatremia complicated by seizure following 3,4-methylenedioxymethamphetamine ingestion. Emergency Medicine Australasia. 2018;30(5):730-731. DOI: 10.1111/1742-6723.13159. Epub 2018 Aug 14
12. Sterns RH, Emmett M, Forman JP. Overview of the treatment of hyponatremia in adults. UpToDate 2019. Available from: https://www.uptodate.com/contents/overview-of-the-treatment-of-hyponatremia-in-adults? search= hyponatremia & source= search result & selected Title= 1~ 150& usage type=default&display_rank=
13. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, et al. Diagnosis, evaluation, and treatment of hyponatremia: Expert panel recommendations. American Journal of Medicine. 2013;126(10 Suppl 1):S1-S42. [Medline]
14. Cotton MA, Ball C, Robinson P. Four simple questions can help screen for eating disorders. Journal of General Internal Medicine. 2003;18(1):53-56. DOI: 10.1046/j.1525-1497.2003.20374.x
15. Skipper A. Refeeding syndrome or refeeding hypophosphatemia. Nutrition in Clinical Practice. 2012;27:34-40. DOI: 10.1177/0884533611427916
16. Parag S, Espiridion ED. Hyponatremia presenting with recurrent mania. Cureus. 2018;10(11):e3645. DOI: 10.7759/cureus.3645