Review (Derleme)

Approach to Hyponatremia in The Elderly Population

Yaşlı Popülasyonda Hiponatremiye Yaklaşım

Dilek TUZUN[1]

[1] Kahramanmaraş Sütçü İmam University, Faculty of Medicine, Department of Endocrinology and Metabolism, Kahramanmaraş, Turkey

Özet

Hiponatremi hem hastanede yatan hastalarda hem de normal popülasyonda en sık görülen elektrolit bozukluğudur. Hiponatremi prevalansı popülasyonda yaklaşık %8'dir ve yaşla birlikte önemli ölçüde artar. Yaşlı hastalarda hiponatremi gelişiminde sıklıkla birden fazla faktör rol oynar. Yaşlıların hiponatremi geliştirme eğilimi, esas olarak yaşlanma ve hiponatremi ile ilişkili ilaçlara ve hastalıklara sık maruz kalma ile ilişkili bozulmuş su atılım kapasitesine bağlanır. Akut semptomatik hiponatremide, serum sodyum seviyelerini akut olarak artırmak ve ciddi nörolojik semptomları önlemek için yaygın olarak hipertonik salin solüsyonu kullanılır. Kronik hiponatremide, serum sodyum konsantrasyonunun düzeltme hızı 10 mEq/L/24 saat ile ve daha güvenli bir şekilde 6-8 mEq/L/24 saat ile sınırlandırılmalıdır. Yaşlı popülasyonda hiponatreminin hem değerlendirilmesi hem de tedavisi zor olduğundan çok dikkatli bir değerlendirme gereklidir.

Anahtar Kelimeler: Hiponatremi, geriatri, ilaçlar

Abstract

Hyponatremia is the most common electrolyte disorder in both hospitalized patients and the normal population. The prevalence of hyponatremia is approximately 8% in the population and increases significantly with age. In older patients, more than one factor often plays a role in the development of hyponatremia. The tendency of the elderly to develop hyponatremia is mainly attributed to impaired water excretion capacity associated with aging and frequent exposure to drugs and diseases associated with hyponatremia. In acute symptomatic hyponatremia, hypertonic saline solution is commonly used to acutely increase serum sodium levels and prevent severe neurological symptoms. In chronic hyponatremia, the rate of correction of serum sodium concentration should be limited to 10 mEq/L/24 h and more safely to 6–8 mEq/L/24 h. Since both the evaluation and treatment of hyponatremia are difficult in the older population, very careful evaluation is required.

Keywords: Hyponatremia, geriatrics, drugs

Yazışma Adresi: Dilek TÜZÜN, Kayseri Yolu 10. km Avşar Kampüsü Kahramanmaraş Sütçü İmam Üniversitesi, 46100, Kahramanmaraş, Türkiye

Phone: +90 344 280 3768 **e-mail:** tuzund@gmail.com

ORCID No: 0000-0002-6693-4928

Submission date: 18.11.2022

Acceptance date: 13.11.2023

DOI: 10.17517/ksutfd.1206810

INTRODUCTION

Hyponatremia is the most common electrolyte disorder in both hospitalized patients and the normal population. The normal plasma sodium range is 135-145mEq/L. Hyponatremia is defined as plasma Na <135mEq/L. Because age is a strong and independent risk factor for hyponatremia, older patients represent a high-risk group for the occurrence of hyponatremia (1).

PREVALENCE AND ETIOLOGY

The prevalence of hyponatremia is approximately 8% in the population and increases significantly with age (2). Hyponatremia incidence is ranging from 15 to 30% among hospitalized patients (3). Studies show that hyponatremia is associated with poor prognosis in older individuals, and hyponatremia is independently associated with an increased risk of mortality. The prevalence of low serum sodium levels is even higher in healthcare settings (4). Miller et al. found that 18% of the 60-year-old population living in a nursing home had hyponatremia. In addition, when multiple serum sodium measurements were made over 12 months, hyponatremia was observed in about half of the patients in at least one episode (5). Similarly, in a prospective study, one-third of the 65-year-old hospitalized patients had serum sodium below 135 mmol/L (6). Zhang et al. (7) retrospectively analyzed inpatient medical records of older patients who were hospitalized and diagnosed with hyponatremia from January 2013 to December 2016. Hyponatremia in older patients hospitalized during the study period They found the prevalence to be 24.7 % (4364/17.693). Of the patients with hyponatremia, 66.0% were classified as mild hyponatremia, 23.8% as moderate hyponatremia, and 10.2% as severe hyponatremia (7). In a study by Zheng et al. (8) hyponatremia was detected in 5.26% of all hospitalized patients during the study period. It was 6.1 % in the older population (8). Cross-sectional population studies show that the incidence increases with age and the reported point prevalence is 7.18% in the elderly versus 2.98% in a younger cohort (9,10).

In older patients, more than one factor often plays a role in the development of hyponatremia. The tendency of older patients to develop hyponatremia is mainly attributed to impaired water excretion capacity associated with aging and frequent exposure to drugs and diseases associated with hyponatremia (11). Drug-induced hyponatremia is often seen in older individuals. Thiazide diuretics, selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), and nonsteroidal anti-inflammatory drugs (NSAIDs) can cause hyponatremia. Diseases alone or in combination with drugs can cause hyponatremia (12). Diuretics are one of the most common causes of hyponatremia in older individuals. Thiazide diuretics are usually associated with hyponatremia, while loop diuretics only occasionally induce hyponatremia. The incidence of thiazide-induced hyponatremia has not been established because additional risk factors for low serum sodium levels are often present. Thiazide-induced hyponatremia is more common in patients with heart failure, liver disease, or malignancy, and those taking high doses of thiazide or taking medications such as NSAIDs, SSRIs, or tricyclic antidepressants (13). Antipsychotic drugs, phenothiazines, butyrophenones, benzodiazepines, and more commonly antidepressants are associated with hyponatremia. SSRIs, SNRIs, and mirtazapine have been reported recently for the majority of cases of hyponatremia related to antidepressants in adults 60 years of age or older. Hyponatremia associated with bupropion, trazodone, and tricyclic antidepressants is less common (14). Factors contributing to the development of hyponatremia associated with psychotropic drugs in older individuals; low body mass index, female gender, low basal serum sodium, concomitant use of other drugs such as diuretics, NSAIDs, proton pump inhibitors, angiotensin converting enzyme inhibitors, angiotensin converting enzyme inhibitors and concomitant heart failure, malignancy, liver disease, or adrenal insufficiency diseases (15). Carbamazepine and oxcarbazepine are the most common antiepileptic drugs (AEDs) associated with hyponatremia. Recently, other AEDs such as eslicarbazepine, sodium valproate, lamotrigine, levetiracetam, and gabapentin have also been reported to induce hyponatremia. Older patients taking valproic acid, phenytoin, or topiramate have a higher risk of hospitalization for hyponatremia compared with those who do not receive an AED (16).

Impaired water excretion capacity associated with aging and frequent exposure to drugs and diseases related to hyponatremia indicate that more than one factor usually plays a role in the development of hyponatremia in older patients. Older individuals are more prone to hyponatremia due to decreased water excretion capacity, mostly due to decreased glomerular filtration rate (GFR) (17). The decreased intrarenal prostaglandin production seen in advanced age may also play a role in the impaired water excretion ability of older individuals. Another contributing factor in older patients is the age-related decrease in total body water percentage (17). Idiopathic inappropriate antidiuretic hormone (SIAD) syndrome is more common in older patients (18). In a prospective study of over 65 years of age, SIAD was shown to be the main factor in half of patients with hyponatremia. It is the most common cause of euvolemic hyponatremia in clinical practice. Under normal conditions, ADH is secreted in response to hyperosmolality and hypovolemia (19).

Hypopituitarism is not an uncommon cause of hyponatremia, especially in patients aged 65 years or older (20). Ishikawa et al.21 reported that 40% of patients aged 65 years and older presenting with hyponatremia had pituitary-adrenal dysfunction (21). Hypopituitarism is more difficult to diagnose in older patients, as symptoms such as fatigue or easy fatigability can be attributed to aging or comorbidities (22).

Diabetes mellitus (DM), infections, heart failure, liver diseases, malignancies, and endocrinopathies should be considered in the etiology of hyponatremia (23). The prevalence of DM is high in the older population. In the case of marked hyperglycemia, serum osmolality increases, resulting in the movement of water out of the cells followed by dilution to lower serum sodium levels. Uncontrolled DM can cause osmotic diuresis and hypovolemic hyponatremia (24).

Decreased protein intake in the older population negatively affects water excretion and may play a role in the development of hyponatremia. In addition, hyponatremia varies seasonally. In summer, the incidence of hyponatremia increases due to more frequent deterioration of kidney functions, decreased salt intake, increased salt loss, and increased water intake (25). "Tea and toast" hyponatremia can be seen in older individuals who have a low GFR, a diet poor in salt and protein, but drink a lot of water. In such cases, there is low distal filtration due to low GFR and possibly chronic sodium deficit. Hyponatremia occurs when water absorption is increased due to a low osmole excretion rate and water consumption exceeds renal water excretion capacity (26).

Pseudohyponatremia occurs in patients with hyperglycemia-induced hyponatremia, hyperproteinaemia, as seen in multiple myeloma and other monoclonal gammopathies or intravenous immunoglobulin administration, and severe hyperlipidemia. Hyperosmolar substances such as radiocontrast, glycine, and mannitol can also cause pseudohyponatremia. Here, although the total sodium amount in the serum does not change, the serum sodium is low as a result of the withdrawal of water from the interstitium into the intravascular area with increased osmolality. Every 0.25 mg/dl increase in serum protein level and 500 mg/dl increase in serum triglyceride level results in a 1mEq/L decrease in serum sodium concentration (27).

SYMPTOMS AND DIAGNOSIS

The normal serum sodium concentration is 135–145 mmol/L. The cut-off concentrations for the definitions of mild, moderate, and severe hyponatremia vary slightly (28). Woodward et al.4 define mild hyponatremia as sodium concentrations from 130 to 135 mmol/L and moderate hyponatremia as 125 to 130 mmol/L; 120 to 125 mmol/L is considered moderately severe if there are no acute symptoms, or severe if symptoms are present; hyponatremia below 120 mmol/L is severe. Mild hyponatremia is often considered to be asymptomatic, yet is associated with subtle cognitive impairments. Symptoms, such as mental confusion, gait disturbance, impaired consciousness, and seizures may occur with increasing severity of hyponatremia. The symptomatology of hyponatremia results from cerebral edema and increased intracranial pressure. The patient may present with nausea, vomiting, headache, weakness, gait and balance disorders, cognitive impairment, confusion, lethargy, convulsions, and coma (29). The symptomatology of acute hyponatremia such as nausea, vomiting, headache, drowsiness, coma, and seizures, and adverse conditions associated with chronic hyponatremia such as fatigue, cognitive impairment, falls, deterioration of bone quality and fracture are more frequent and severe in older patients (30).

Medications are among the most common causes of hyponatremia. Although the time of onset of drug-induced hyponatremia varies greatly, it often occurs within the first few weeks after the start of treatment. Therefore, the occurrence of low serum sodium levels in a patient after taking the drug for a long period, and the presence of an additional predisposing and/or added hyponatremia factor should be suspected. Thiazide diuretics are among the most common causes of drug-induced hyponatremia. Increased potassium excretion is a useful marker for the diagnosis of thiazide-induced hyponatremia (31).

In the evaluation of hyponatremia, especially in older individuals, hypopituitarism, especially secondary adrenal insufficiency, should be investigated. Hypopituitarism and to a lesser degree, primary adrenal insufficiency are causes of hyponatremia that cannot be directly differentiated from SIAD by routine laboratory studies and volume status assessment therefore, measurement of relevant laboratory parameters is mandatory for the diagnosis of hypothalamic-pituitary-adrenal axis disorders (32). Cortisol is a physiological inhibitor of antidiuretic hormone (ADH). Hyponatremia should be attributed to inappropriate ADH release due to hypocortisolism (23). Uric acid appears to be a valuable index for assessing extracellular fluid volume during hyponatremia. During the expansion of extracellular fluid volume, such as SIADH and hypocortisolism, renal proximal uric acid reabsorption in the tubule is inhibited, therefore low serum concentration and high fractional excretion are observed (23). Patients with adrenal insufficiency cannot be easily identified by routine

laboratory studies, and endocrine parameters should be determined for the diagnosis of hypothalamic-pituitary-adrenal axis disorders. Specifically, a morning serum cortisol greater than or equal to 18 µg/dL concentrations of less than or equal to 3 µg/dL strongly suggest the diagnosis. In all other cases, dynamic testing is necessary (33). The brief ACTH stimulation test represents the first step in the diagnostic workup. 250 µg corticotropin serum cortisol 30-60 minutes after intravenous administration elevation of its concentration to a peak of 18 µg/dL or more indicates a normal response to the high-dose ACTH stimulation test (34,35). In cases of severe secondary adrenal insufficiency, there may be a slight or no increase in serum cortisol levels after corticotropin administration. In patients with mild or new-onset secondary adrenal insufficiency, the test may result in normal results, as the 250 µg ACTH dose given represents a supraphysiological stimulus. In such cases, the insulin hypoglycemia test is more reliable (23). However, the insulin hypoglycemia test is contraindicated in patients with epilepsy and coronary artery disease, and in patients over 60 years of age. It is more appropriate to perform a low-dose (1 µg) ACTH stimulation test in patients with suspected secondary adrenal insufficiency (23,35). Serum Adrenocorticotropic Hormone (ACTH) level is the best parameter to distinguish between primary and secondary adrenal insufficiency. In primary adrenal insufficiency, serum cortisol levels are low and ACTH levels are usually above 100 pg/mL. In secondary adrenal insufficiency, low normal serum ACTH levels are observed (23).

Hypothyroidism is more common among older people because of the increased incidence and prevalence of autoimmune thyroiditis. For the diagnosis of SIAD, thyroid and adrenal tests must be shown to be normal. However, hyponatremia due to hypothyroidism is extremely rare and probably only occurs in severe hypothyroidism. If normonatremia cannot be achieved with thyroid hormone replacement in older patients with TSH <50 mIU/mL, idiopathic SIAD should be considered in the differential diagnosis. Even in myxedema coma, other possible causes of hyponatremia should be investigated in detail (36). Hypothyroidism can result from a defect anywhere in the hypothalamic-pituitary-thyroid axis. It is mostly caused by diseases of the thyroid gland. Much less frequently, it is caused by decreased thyrotropin (TSH) secretion from the anterior pituitary gland or the hypothalamus. It is caused by a decrease in thyrotropin-releasing hormone (TRH). Patients may be asymptomatic or rarely present with coma (37). Warner et al38. showed a statistical association between hyponatremia and hypothyroidism: for every 10 mU/L rise in thyroid-stimulating hormone, serum sodium decreased by 0.14 mmol/L (38).

Postural changes in blood pressure and hypovolemic orthostatic hypotension may often indicate autonomic dysfunction, medications, or other systemic disease; therefore, it is difficult to distinguish between hypovolemic and euvolemic hyponatremia on clinical grounds alone in older patients. Urinary sodium concentration should be measured in patients with hyponatremia, urinary sodium concentration <30 mmol/L strongly indicates hypovolemia. However, low urinary sodium concentration may not be observed in older persons with slow adaptive mechanisms (39). Urine sodium levels >30 mmol/L, hypouricemia (4 mg/dL), and urea levels <20 mg/dl are seen in SIAD. But older people often go on a low-salt diet or suffer from anorexia and under these conditions, patients with chronic SIAD may have urinary sodium levels<30 mmol/L. Therefore, the differences between hypovolemic hyponatremia and SIAD are often difficult in older individuals. In such cases, administration of 1-2 liters/day of normal saline for 2 days provides a significant clue. 5 mmol/L increase in serum sodium level is associated with a <0.5% increase in fractional excretion of sodium (FeNa). When combined, it is highly suggestive of hypovolemic hyponatremia. In contrast, a >0.5% increase in FENa+ and an increase of <5 mmol/L are indicative of SIAD (40).

TREATMENT

Eliminating possible causes of hyponatremia is an essential part of treatment. A medication review of the patient should be carried out and careful consideration should be given to substituting, reducing the dose, or stopping medications associated with low sodium. Discontinuation of drugs can be combined with an isotonic saline infusion with careful monitoring of the clinical and biochemical response (40). In acute symptomatic hyponatremia, hypertonic saline solution (3%) is commonly used to acutely increase serum sodium levels and prevent severe neurological symptoms. In cases of acute symptomatic hyponatremia, raising the acute serum sodium concentration by 4-6 mEq/L within 4-6 hours is recommended to reverse symptoms. Hypovolemic hyponatremia is treated with adequate fluid resuscitation to reduce the stimulus for ADH secretion. Normal saline is usually used to suppress the hypovolemic stimulus for ADH release (41,42). In patients with SIAD, discontinuation of suspected drugs and reduction of water consumption and hypertonic fluids may be necessary. In these situations, 20-40 mg intravenous furosemide may also be administered to prevent circulatory overload, particularly in older individuals if there is concomitant cardiac dysfunction. Furosemide increases free water excretion and contributes to serum

sodium elevation. Vaptans (vasopressin-2 antagonists) are a class of drugs that selectively antagonize the antidiuretic effect of vasopressin leading to increased water diuresis. These drugs can be used in patients with chronic symptomatic euvolemic hyponatremia and, in some countries, in patients with hypervolemic hyponatremia (22). The appropriate rate of correction of serum sodium levels is very important for patients with hyponatremia. Over-correction of serum sodium concentration may lead to osmotic demyelination syndrome (ODS), especially in alcoholic individuals and patients with hypokalemia, malnutrition, or advanced liver disease (43). In chronic hyponatremia, even symptomatic, the rate of correction of serum sodium concentration should be limited to 10 mEq/L/24h and more safely to 6–8 mEq/L/24 h. Frequent determination of serum sodium concentration (every 4-6 hours) and appropriate adjustment of the correction rate in patients at high risk of developing ODS are strongly recommended (44).

CONCLUSION

Hyponatremia is a common finding in the older population due to the presence of factors contributing to increased ADH and the frequent prescription of hyponatremia-related drugs such as thiazides or antidepressants. Since both the evaluation and treatment of hyponatremia are difficult in the older population, careful evaluation is required.

REFERENCES

1. Ioannou P, Panagiotakis S, Tsagkaraki E, Tsioutis C, Fragkiadakis K, Gikas A, et al. Increased Mortality in Elderly Patients Admitted with Hyponatremia: A Prospective Cohort Study. J Clin Med. 2021;10:10(14):3059.
2. Liamis G, Rodenburg EM, Hofman A, Zietse R, Stricker BH, Hoorn EJ. Electrolyte disorders in community subjects: prevalence and risk factors. Am J Med. 2013;126(3):256–263.
3. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. Am J Med .2006;119:0-35.
4. Woodward M, Gonski P, Grossmann M, Obeid J, Scholes R, Topliss DJ. Diagnosis and management of hyponatremia in the older patient. Intern Med J. 2018; 48(Suppl 1): 5-12.
5. Miller M. Hyponatremia: age-related risk factors and therapy decisions. Geriatrics. 1998 ;53(7):32-3.
6. Frenkel WN, van den Born BJ, van Munster BC, Korevaar JC, Levi M, de Rooij SE. The association between serum sodium levels at the time of admission and mortality and morbidity in acutely admitted elderly patients: a prospective cohort study. J Am Geriatr Soc. 2010;58(11):2227–2228.
7. Zhang X, Li XY. Prevalence of hyponatremia among older inpatients in a general hospital. Eur Geriatr Med. 2020;11(4):685-692.
8. Zheng Y, Zheng FP, Li H. The prevalence and causes of hyponatremia in hospitalized patients. 2020 1;59(1):29-34.
9. Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. Clin Chim Acta. 2003;337:169-172.
10. Siregar P. The risk of hyponatremia in the elderly compared with younger in the hospital inpatient and outpatient. Acta Med Indones. 2011;43:158-161.
11. Filippatos TD, Makri A, Elisaf MS, Liamis G. Hyponatremia in the elderly: challenges and solutions. Clin Interv Aging. 2017;12:1957-1965.
12. Rosner MH. Severe hyponatremia associated with the combined use of thiazide diuretics and selective serotonin reuptake inhibitors. Am J Med Sci. 2004:327(2):109-11.
13. Falhammar H, Skov J, Calissendorff J, Nathanson D, Lindh JD, Mannheimer B. Associations Between Antihypertensive Medications and Severe Hyponatremia: A Swedish Population-Based Case-Control Study. J Clin Endocrinol Metab. 2020 Oct 1;105(10):e3696–705. doi: 10.1210/clinem/dgaa194. Erratum in: J Clin Endocrinol Metab. 2020 Oct 1;105(10): PMID: 32285124; PMCID: PMC7451505.
14. De Picker L, Van Den Eede F, Dumont G, Moorkens G, Sabbe BG. Antidepressants and the risk of hyponatremia: a class-by-class review of literature. Psychosomatics. 2014 Nov-Dec;55(6):536-47.
15. Viramontes TS, Truong H, Linnebur SA. Antidepressant-induced hyponatremia in older adults. Consult Pharma. 2016;31(3):139–150.
16. Berghuis B, Hulst J, Sonsma A, McCormack M, de Haan GJ, Sander JW, et al. Symptomatology of carbamazepine- and oxcarbazepine-induced hyponatremia in people with epilepsy. Epilepsia. 2021 Mar;62(3):778-784.
17. Nagler EV, Vanmassenhove J, van der Veer SN, Nistor I, Van Biesen W, Webster AC, et al. Diagnosis and treatment of hyponatremia: a systematic review of clinical practice guidelines and consensus statements. BMC Med. 2014 Dec 11;12:1.
18. Kounatidis D, Liakopoulou C, Brozou V, Dimopoulou G, Vallianou N. Chronic idiopathic hyponatremia in an elderly patient due to inappropriate antidiuretic hormone secretion (SIADH) syndrome. Hippokratia. 2019 Jan-Mar;23(1):42-44.
19. Anpalahan M. Chronic idiopathic hyponatremia in older people due to syndrome of inappropriate antidiuretic hormone secretion (SIADH) possibly related to aging. J Am Geriatr Soc. 2001;49(6):788–792.
20. Foppiani L, Ruelle A, Bandelloni R, Quilici P, Del Monte P. Hypopituitarism in the elderly: multifaceted clinical and biochemical presentation. Curr Aging Sci. 2008;1(1):42–50.
21. Ishikawa Se, Saito T, Fukagawa A, Higashiyama M, Nakamura T, Kusaka I, et al. Close association of urinary excretion of aquaporin-2 with appropriate and inappropriate arginine vasopressin-dependent antidiuresis in hyponatremia in elderly subjects. J Clin Endocrinol Metab. 2001 Apr;86(4):1665-71. doi: 10.1210/jcem.86.4.7426. PMID: 11297601.
22. Shapiro DS, Sonnenblick M, Galperin I, Melkonyan L, Munter G. Severe hyponatraemia in elderly hospitalized patients: prevalence, aetiology and outcome. Intern Med J. 2010;40(8):574–580.
23. Liamis G, Milionis HJ, Elisaf M. Endocrine disorders: causes of hyponatremia not to neglect. Ann Med. 2011 ;43(3):179-87.
24. Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Intensive Care Med. 2014;40(3):320-31.
25. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013 ;126(10 Suppl 1):S1-42.

26. Thaler SM, Teitelbaum I, Berl T. "Beer potomania" in non-beer drinkers: effect of low dietary solute intake. Am J Kidney Dis. 1998;31(6):1028–1031.
27. Kim GH. Pseudohyponatremia: does it matter in current clinical practice? Electrolyte Blood Press. 2006;4(2):77-82.
28. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013 Oct;126(10 Suppl 1):S1-42
29. Dineen R, Thompson CJ, Sherlock M. Hyponatraemia - presentations and management. Clin Med (Lond). 2017;17(3):263-269.
30. Gankam Kengne F, Decaux G. Hyponatremia and the Brain. Kidney Int Rep. 2017 Sep 1;3(1):24-35.
31. Hix JK, Silver S, Sterns RH. Diuretic-associated hyponatremia. Semin Nephrol. 2011 Nov;31(6):553-66. doi: 10.1016/j.semnephrol.2011.09.010. PMID: 22099512.
32. Diederich S, Franzen NF, Bähr V, Oelkers W. Severe hyponatremia due to hypopituitarism with adrenal insufficiency: report on 28 cases. Eur J Endocrinol. 2003;148(6):609-17.
33. Grinspoon SK, Biller BM. Clinical review 62: laboratory assessment of adrenal insuffi ciency. J Clin Endocrinol Metab. 1994;79:923- 31.
34. Hockings GI, Nye EJ, Grice JE, Jackson RV. Short synacthen test versus insulin stress test for the assessment of the hypothalamo-pituitary axis: controversy revisited again. Clin Endocrinol (Oxf). 1997;46:775- 6.
35. Karaca Z, Grossman A, Kelestimur F. Investigation of the Hypothalamo-pituitary-adrenal (HPA) axis: a contemporary synthesis. Rev Endocr Metab Disord. 2021 Jun;22(2):179-204.
36. Liamis G, Filippatos TD, Liontos A, Elisaf MS. Management of endocrine disease: Hypothyroidism-associated hyponatremia: mechanisms, implications and treatment. Eur J Endocrinol. 2017;176(1):R15-R20.
37. Devdhar M, Ousman YH, Burman KD. Hypothyroidism. Endocrinol Metab Clin North Am. 2007;36:595- 615
38. Warner MH, Holding S, Kilpatrick ES. The effect of newly diagnosed hypothyroidism on serum sodium concentrations: a retrospective study. Clin Endocrinol (Oxf). 2006;64: 598 – 9.
39. Hato T, Ng R. Diagnostic value of urine sodium concentration in hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion versus hypovolemia. Hawaii Med J. 2010;69(11):264-267.
40. Milionis HJ, Liamis GL, Elisaf MS. The hyponatremic patient: a systematic approach to laboratory diagnosis. CMAJ. 2002;166(8):1056-1062.
41. Soiza RL, Talbot HS. Management of hyponatraemia in older people: old threats and new opportunities. Ther Adv Drug Saf. 2011 ;2(1):9-17.
42. Schrier RW, Bansal S. Diagnosis and management of hyponatremia in acute illness. Curr Opin Crit Care. 2008;14(6):627-634.
43. Hoorn EJ, Zietse R. Diagnosis and Treatment of Hyponatremia: Compilation of the Guidelines. J Am Soc Nephrol. 2017;28(5):1340-1349.
44. Sterns RH. Treatment of Severe Hyponatremia. Clin J Am Soc Nephrol. 2018;13(4):641-649.